Synthesis of Polyaryl and Functionalized Pyrene Scaffolds *via* C-H Functionalization

A thesis submitted for the partial fulfilment

of the degree of Doctor of Philosophy

By

Arup Dalal

Department of Chemical Sciences

Indian Institute of Science Education and Research (IISER) Mohali

Knowledge City, Sector 81, SAS Nagar, Mohali,

Manauli PO, 140306, Punjab, INDIA

April, 2024

Dedicated to

My Beloved Parents and Dada..

Declaration

I hereby declare that matter embodied in this thesis entitled **''Synthesis of Polyaryl and Functionalized Pyrene Scaffolds *via* C-H Functionalization''** is the result of investigations carried out by me under the supervision of Prof. S. Arulananda Babu at the Department of Chemical Sciences, Indian Institute of Science Education and Research (IISER) Mohali, India. This work has not been submitted in part or full for the award of any degree, diploma, or fellowship to any other university or institute. Whenever contributions of others are involved, every effort is made to indicate it clearly with due acknowledgments. In keeping with the general practice of reporting scientific observations, acknowledgments 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 judgment is regretted. A complete bibliography of the books and journals referred to is given at the end of the thesis.

Arup Dalal

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

Professor

Department of Chemical Sciences

Indian Institute of Science Education and Research Mohali

Date:

Place:

Acknowledgments

I am deeply grateful to many people without whom this thesis would not have been possible. First and foremost, I would like to convey my sincere gratitude towards my supervisor Professor S. Arulananda Babu for guiding me through my Ph.D. He has been extremely patient with me, from discussing monthly work report to giving feedback on my data writing as well as my bench-work. He has shaped me as scientist. He is an incredible mentor who has encouraged me and believed in me even when I did not. His knowledge of the field, positivity towards the research, and his advice both professional and personal have guided me throughout my journey. I strongly believe that the experience I have got from his suggestions and comments will help me in future.

I thank Prof. R. Vijaya Anand & Dr. Sugumar Venkataramani (DC members), and Prof. S. S. V. Ramasastry for their valuable suggestions during yearly assessments.

I express my sincere thanks to all my teachers since my childhood.

I must not miss the opportunity to thank my dada, Dr. Urmibhusan Bhakta, who has been my inspiration since I was a kid. Thanks a lot, big brother, for inspiring me, keeping me motivated, and supporting me.

I express my gratitude to both my past and current lab members. I thank to my older colleagues Dr. Naveen, Dr. Ramarao, Dr. Gopalakrishnan, and Dr. Sankar. Specially I appreciate Dr. Narendra and Dr. Padmavathi for their continuous support and guidance throughout my journey. I also want to acknowledge my colleagues, Dr. Radha, Dr. Prabhakar, and Debabrata, who motivate me every day. Radha stays strong in every situation, Prabhakar works hard, and Debu remains calm – all of which inspire me. A heartfelt thank you to my younger colleagues, Raman for assistance during the final stages of my Ph.D. and for being inspiration with her hardworking mentality, Shefali for assistance in biphenyl project, Sonam for being a good padosi and providing assistance. Gratitude to Yashika, Pooja, and Urja for their constant help whenever needed. Special thanks to my juniors Amit, Subhankar (for assistance in two projects), Amit Jangra, and Harcharan for their overall helpfulness during this phase.

I thank present and former Director, former and present HOD, Dept. of Chemical sciences, all faculty members.

I want to express my gratitude to the Director of IISER Mohali, for giving me the resources and support to do my research. I appreciate the NMR, X-ray, HRMS, Library, and Computing facilities at IISER Mohali. I also want to thank the Head of the Department of Chemical Sciences for letting me use the single crystal X-ray facility and other departmental resources. Special thanks to all the technicians and teaching staff at IISER Mohali, including Mr. Balbir (NMR), Mr. Triveni (HRMS), Mr. Mangat, Mr. Prahlad, and Mr. Bahadur for their assistance.

I am highly thankful to the post-doctoral fellows Dr. Gowri, Dr. Dipti, Dr. Vinod and Dr. Panduranjan for their valuable suggestions.

I thank all the summer project students: Kavin, Deepak, Himanshu, Shounak, Anoop, Bubul, Neelmani, Ajay, Shahil, Neetu, Sourabh, Gurkeerat, and Rajib.

Thanks to my friend Dr. Diksha for all the support and encouragement from the beginning days.

I am deeply expressing my thanks to Debu for everything throughout this journey, my brigade group: Debu, Madhu, Abhishek, Raj, Subhendu, Sudipto and Kuntal for making this journey easier. My heartfelt thanks to my batchmates Dr. Shaina, Dr. Paveet, Prateek, and Dr. Saisrinivas, for all the lighter moments.

I thank my HCU seniors and friends: Dr. Raja, Dr. Sugata, Dr. Joy, Dr. Rajib for all the support and care. I thank my school friends Sunny and Gopan for all lovely moment. I express my thank to my bhai Soumik and Rahul for their love and support.

I want to express my heartfelt thanks to my family – Baba, Maa, and Runu – for supporting, loving, and caring for me as I pursue my dream. I thank Tapas for being with me always. A special thanks to my Dadu for always encouraging me to follow my dreams. Thank you, Dadu. I'm sincerely grateful to my uncles (Borokaka and Chotokaka) and maternal uncles for their unconditional love.

In the end, I'm grateful to everyone who helped me reach my dreams.

List of publications from this thesis work:

1. **Dalal, A**.; Singh, P.; Babu, S. A.* *Tetrahedron* **2019**, *75*, 1246.

   Title: One-pot, solvent-free Pd(II)-catalyzed direct *β*-C-H arylation of carboxamides involving anhydrides as substrates *via in situ* installation of directing group.

2. **Dalal, A**.; Babu, S. A.* *Synthesis* **2021**, *53*, 3307.

   Title: Pd(II)-catalyzed directing group-aided C-H arylation and alkylation of pyrene core: Synthesis of C1,C2- and C1,C10-disubstituted pyrene motifs.

3. **Dalal, A**.; Babu, S. A.;* Banga, S. *Asian J. Org. Chem.* **2023**, e202300508.

   Title: Assembling of Polyaryls (Terphenyls, Tetraphenyls, Pentaphenyls, and Hexaphenyls) through Pd(II)-catalyzed C−H Arylation of Biaryl Carboxamides with Iodobiaryls.

4. **Dalal, A**.; Bodak, S.; Babu, S. A.* *Org. Biomol. Chem.* **2024**, *22*, 1279.

   Title: Picolinamide-assisted *ortho*-C-H functionalization of pyrenylglycine derivatives using aryl iodides.

List of Publications as a co-author:

1. Singh, P.; **Dalal, A**.; Babu, S. A.* *Asian J. Org. Chem*. **2019**, *8*, 877.

   Title: Palladium(II)-Catalyzed Sp^3/Sp^2 *γ*- and *δ*-C-H Functionalization of Aryl Amines using 5-Methylisoxazole-3-Carboxamide as Directing Group.

2. Babu, S. A.;* Padmavathi, R.; Suwasia, S.; **Dalal, A**.; Bhattacharya, D.; Singh, P.; Tomar, R. *Studies in Natural Products Chemistry* **2021**, *71*, 311.

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

3. Reji, R.; Tripathi, N. P.; Rani, K.; **Dalal, A**.; Babu, S. A.; Sengupta, S.* *Chemistryselect*, **2021**, *6*, 12022.

   Title: Structure-Property Correlation of C10-(H)-Arylated-N-(pyren-1-yl)-picolinamide Regioisomers towards Cu^{2+} and Fe^{3+} Sensing.

4. Tomar, R.; Kumar, A.; **Dalal, A**.; Bhattacharya, D.; Singh, P.; Babu, S. A.* *Asian J. Org. Chem.* **2022**, 11, e202200311.

   Title: Expanding the Utility of Inexpensive Pyridine-N-oxide Directing Group for the Site-Selective sp^2/sp^3 γ-C-H and sp^2 δ-C-H Functionalization of Carboxamides.

5. Babu, S. A.;* **Dalal, A**.; Bodak, S. *Chemistry* **2023**, *5*, 2713.

   Title: Recent Advances in C–H Functionalization of Pyrenes.

Conferences/Symposia:

1. Participated in the Recent Advances in Organic and Biomolecular Chemistry (RAOBC 2019) held at Indian Institute of Science Education and Research Mohali, India (22-24 March, 2019).
2. Participated in 1st CRIKC Symposium (CCS 2019) held at IISER Mohali, Punjab, India. (2^{nd} & 3^{rd} November, 2019)
3. Participated in the 27th CRSI-National Symposium in Chemistry held at IISER Kolkata, India. (26^{th} to 29^{th} September, 2021)
4. Poster Presentation entitled "*Pd(II)-catalyzed C-H arylation and alkylation of pyrene core: Synthesis of C1,C2- and C1,C10-disubstituted pyrene motifs*", is presented in an online national conference on organic chemistry at the NITT Organic Chemistry Conference '21 (NITTOCC) held at NIT Trichy, Tamil Nadu, India. (November 16th to 18th December, 2021) (**Best Poster Presentation Award**)
5. Poster Presentation entitled "*Pd(II)-catalyzed C-H arylation and alkylation of pyrene core: Synthesis of C1,C2- and C1,C10-disubstituted pyrene motifs*", at the 29th CRSI-National Symposium in Chemistry held at IISER Mohali, India. (7^{th} to 9^{th} July, 2022)
6. Participated in the *Recent Advances in Bioorganic and Medicinal Chemistry (RABMC 2022)* held at the National Institute of Pharmaceutical Education and Research (NIPER) Mohali, India (19th November, 2022).

Preamble

Some cross-coupling reactions involve the preparation and utilization of pre-functionalized starting materials, leading to lengthy syntheses and the generation of unwanted waste. In contrast, a more environmentally friendly approach has emerged, involving the activation of otherwise inert carbon-hydrogen (C-H) bonds. This method allows for the use of less pre-functionalized raw materials, significantly improving the efficiency and atom economy of organic syntheses. Additionally, it enables new disconnection approaches in retro-synthetic analysis, making it possible to utilize a broader range of readily available and renewable starting materials. Motivated by the advantages and effectiveness of this process, the goal of this thesis is to synthesize polyaryl (important precursor in bioactive molecules as well as in material sciences) and functionalized pyrene motifs (a crucial motif in material sciences) using palladium-catalyzed bidentate directing group-assisted functionalization of carbon-hydrogen (C-H) bonds.

Chapter 1 deals with the fundamental principles of C-H activation, along with its importance, related techniques, and mechanistic characteristics**.** Since the majority of the thesis focuses on the synthesis of biaryl as well as polyaryl moieties using directing group-assisted C-H activation methods, some literature reports regarding the synthesis of biaryl motifs using transition metal-catalyzed C-H activation methods have been discussed.

Chapter 2 explores a one-step, multicomponent, solvent-free process involving Pd(II)-catalyzed direct *β*-C-H arylation of carboxamides. This method incorporates anhydrides as substrates and involves the *in situ* installation of directing groups (DG). Typically, the DG-assisted *β*-C-H activation/arylation of carboxamides is a two-step procedure that includes DG installation followed by Pd(II)-catalyzed C-H arylation. we pursued a multicomponent-type reaction incorporating an anhydride, a directing group (e.g., 8-aminoquinoline), an aryl iodide, a Pd(II) catalyst, and a suitable additive.

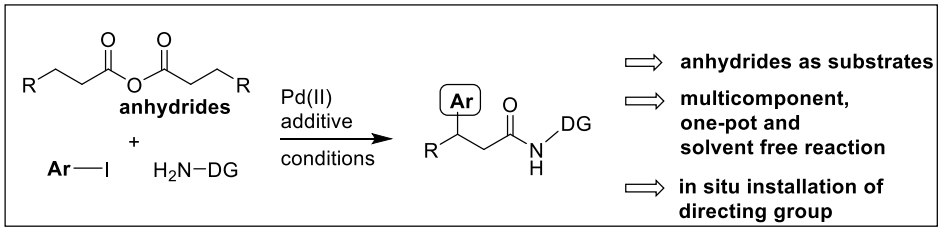
Chapter 3 focuses on assembling polyaryls motifs *via* arylation of biaryl carboxamides with iodobiaryls. Biaryl-based compounds serve as foundational structures, playing a crucial role in numerous drug molecules, natural products, bioactive synthetic compounds and organic functional materials. In our study, we introduced a novel method using Pd(II)-catalyzed bidentate directing group (DG)-assisted C-H arylation. This innovative approach enables the construction of polyaryl motifs, specifically π-extended biaryls, in a single operation, utilizing biaryl-based carboxamides and iodobiaryls as coupling partners.

Chapter 4 describes the utilization of Pd(II)-catalyzed directing group-aided C-H arylation/alkylation to functionalize the pyrene core. This specifically targets the challenging C2 and K-region C10 positions of the pyrene core. Our focus is on expanding the collection of pyrene derivatives by introducing C1,C2- and C1,C10-disubstituted pyrene motifs.

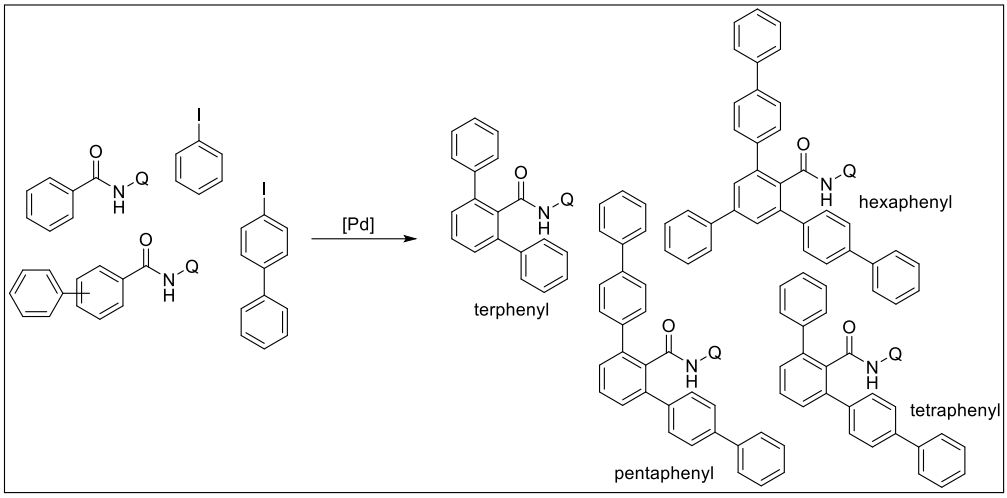
Chapter 5 demonstrates the development of novel pyrenylglycine scaffolds containing the picolinamide moiety *via* the Ugi multicomponent reaction. This compound, features the picolinamide moiety, undergoing Pd(II)-catalyzed C(2)-H arylation at the non-K-region, resulting in the generation of a diverse collection of novel C(2)-H arylated pyrenylglycines. Furthermore, small peptides based on pyrenylglycine were synthesized using these C(2)-arylated pyrenylglycines.

Objectives

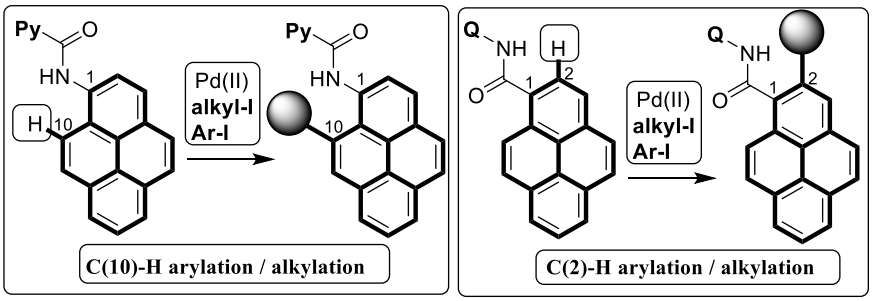
1) Directing group-assisted C-H activation/functionalization methodology is one of the promising ways to achieve C-C, C-O, C-N, C-X bonds, etc. In many instances, the use of directing groups (DG) is deemed unfavourable for synthetic efficiency due to the extra effort involved in both installing and removing them. Consequently, there is a growing interest in developing more optimal synthetic strategies based on C–H activation that align with the principles of atom economy and step economy. Having thought in mind, a part of the thesis empathized on the construction of *β*-arylated aliphatic carboxamides as well as *ortho*-arylated aromatic carboxamides involving anhydride as substrate *via in situ* installation of directing group.



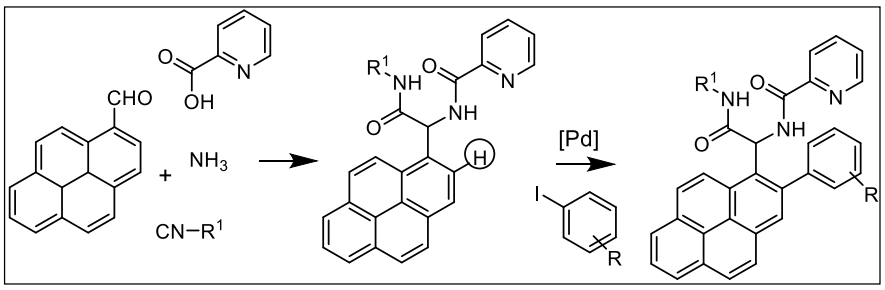
2) π-extended biaryls or polyphenylenes (e.g., teraryls, quateraryls, penta-aryls, hexa-aryls, etc.), have garnered significant attention in the realms of organic, materials, and medicinal chemistry research. Therefore, a part of the thesis work contributes to assembling libraries of polyaryls (terphenyls, tetraphenyls, pentaphenyls and hexaphenyls) *via* the C-H activation strategy.



3) Pyrene and its derivatives have become the focus of considerable interest across diverse domains of chemical sciences, encompassing organic chemistry, supramolecular chemistry and materials chemistry because of their exceptional fluorescence characteristics, effective excimer emission and elevated charge carrier mobility. Motivated by the significance of pyrene, this part of the thesis work is focused on the synthesis of C1,C2 and C1,C10 di-substituted pyrene derivatives using C-H activation methodology.



4) The synthesis and biological evaluation of unnatural amino acid derivatives (non-proteinogenic amino acid derivatives) is a significant area of interest related to chemical biology and drug discovery research. This part of the thesis work aims to synthesize of *ortho*-arylated pyrenylglycine (pyrene-based glycine) derivatives using picolinamide-assisted C-H functionalization strategy.



Chapter 1

Introduction to transition metal catalyzed C-H Activation/functionalization.

The synthesis of new molecules has offered our society new drugs to cure diseases, materials like plastics, new dyes to color clothes, etc. Since urea can now be synthesized in labs, synthetic organic chemists have devoted their careers to developing new, beneficial compounds for humanity. The main aim of a synthetic organic chemist is to develop a new methodological aspect that is comparatively less cost-effective, and greener towards the environment compared to the previously known method.

Organic compounds consist of carbon frameworks and have numerous C-H bonds. Traditional organic reactions usually create new molecules by changing different functional groups. Until 1980, most challenging tasks for organic chemists was synthesizing C-C and C-X (X = O, N, etc.) bonds by breaking C-H bonds. This was difficult due to the high energy required to break these bonds and their high acidity (as indicated in table 1). Despite a few reports in the literature, these were not seen as the typical ways organic chemists activate and modify C-H bonds.[1]

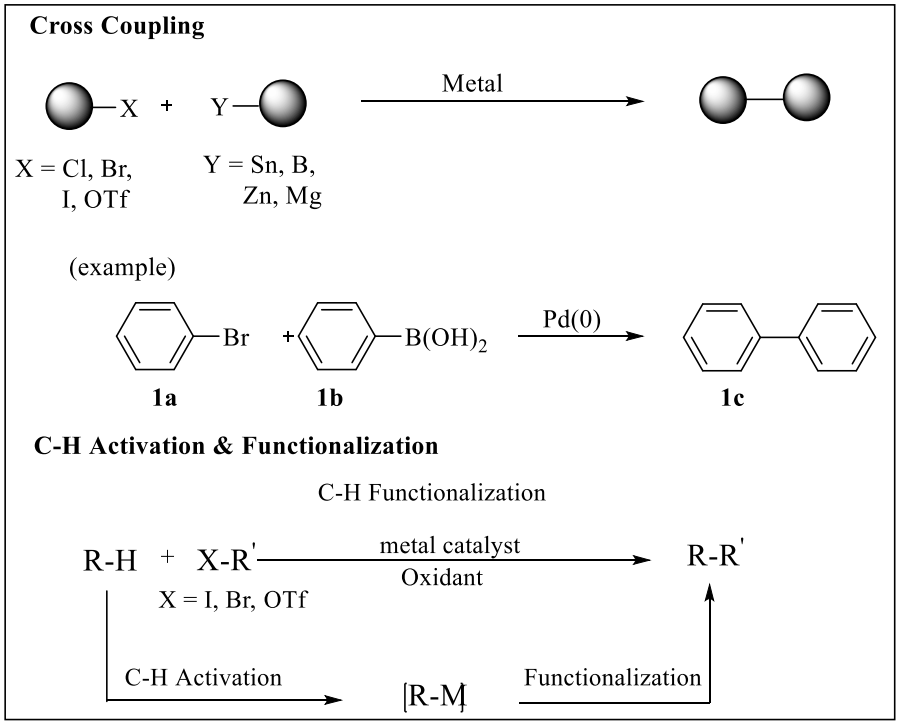
Cross-Coupling Reaction: The famous C-C coupling reactions (Noble Prize, 2010) were developed around the 1980s. However, these methods necessitate the synthesis and utilization of pre-functionalized starting materials, leading to prolonged synthetic processes and the generation of undesirable products (Scheme 1).

Bond	Bond Dissociation Energy (Kcal/mol)	pK_a (water)
CH_3-H	103	48
$(CH_3)_2CH$-H	95	51
$(CH_3)C$-H	93	53
CH_2=CH-H	112	50
C_6H_5-H	110	43
CH_2=$CHCH_2$-H	88	43
$C_6H_5CH_2$-H	85	41

Table 1: Dissociation energy of various C-H bonds.

For example, if we consider the Suzuki cross-coupling reaction, the reaction takes place between boronic acid and aryl halide to form a C-C cross-coupling product. So, synthesizing boronic acid is the pre-functionalization step here. Hence, direct functionalization of C-H bonds provides an attractive alternative to the C-C coupling reactions.[2,3]

C-H activation and functionalization: C-H activation and C-H functionalization methodology is a subject of discussion for many decades. In general, the C-H bond cleaved by transition metal by forming the C-TM intermediate is called the C-H activation step, where TM represents the transition metal. C-TM intermediate further involves the formation of the desired product through a reductive elimination step, which is called C-H functionalization.[4] (Scheme 1)



Scheme 1: Cross-coupling reaction *vs* C-H activation method.

Therefore, we can say that the C-H functionalization reaction occurs *via* the C-H activation step. The C-H activation step depends upon the reactivity of substrates and metal catalysts being used (e.g., SEAr for the case of an electron rich aromatic substrate and an electrophilic metal centre). However, C-H activation may not necessarily lead to a C-H functionalization. It is a possibility that the C-H bond is activated reversibly, but no new functional group is installed.[4]

There are many ways to activate the C-H bond. In this thesis we mainly discussed transition metal catalysed C-H bond activation. Metal catalysed C-H bond activation reaction may divide mainly into three parts:

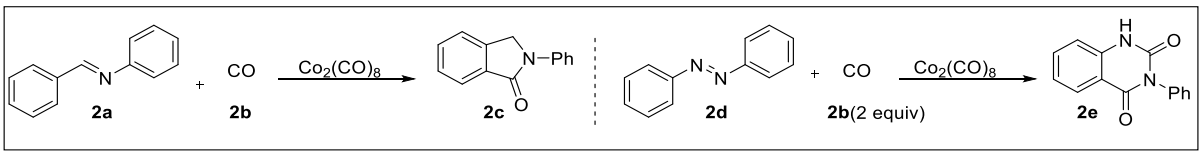
- Direct C-H bond activation.
- Directing group-assisted C-H bond activation.
- Transient directing group assisted C-H bond activation.

The general mechanism is as follows: at first metal co-ordinates with the substrate and activates the C-H bond. This is followed by oxidative addition step. Transmetallation and reductive elimination are the last two steps respectively to give the desired C-H functionalized product.

- **Direct C-H bond activation:** Direct C-H functionalization involves activating a C-H bond without relying on any functional or directing groups. However, when applying this method to molecules with multiple C-H bonds, challenges in regioselectivity arise, as electronic and steric factors govern the outcome.
- **Directing group-assisted C-H bond activation:** A simple aromatic or aliphatic molecule, contain multiple different and equivalent hydrogen atoms. Directing groups are introduced in substrates, which direct the metal to activate the desired C-H bond to obtain a regio-selective and stereo-selective final product.
- **Transient directing group assisted C-H activation:** To address the issue of DG removal, easily removable and/or modifiable DGs have been developed for organic synthesis. The reversible *in-situ* generation and deconstruction of the DG in a transient manner have the potential to reduce laborious synthetic operations in substrates.

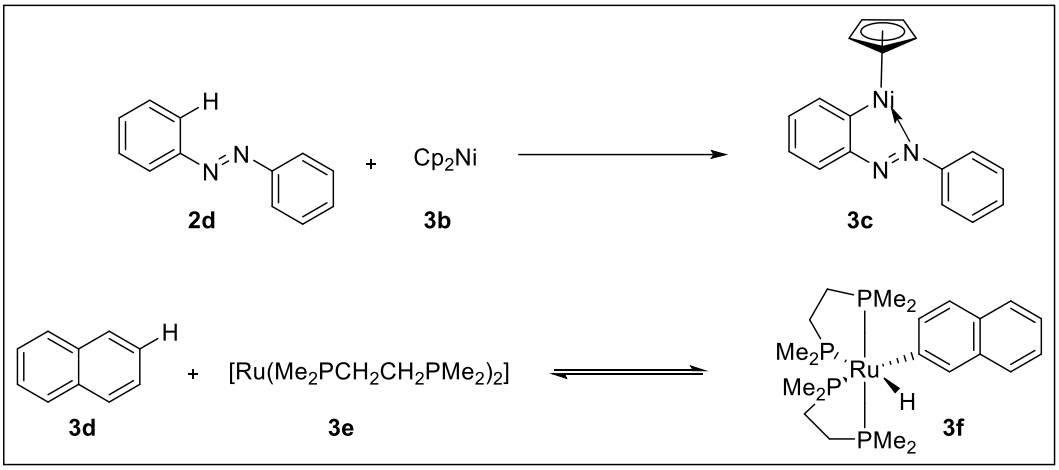
This thesis mainly demonstrates the directing group-assisted transition metal catalyzed (mainly Pd) C-H bond activation and functionalization reactions. Before going into detail, we will briefly discuss some pioneering literature regarding transition metal catalyzed C-H activation reactions.[4]

In the last few decades, a lot of work has been done in the field of C-H activation to achieve synthetically useful products. We tried to include some pioneering reports which are considered representative of establishing the field. In 1955 and 1956, Murahashi first reported Co catalyzed insertion of C=O into aldimine and azobenzene.[5] (Scheme 2)



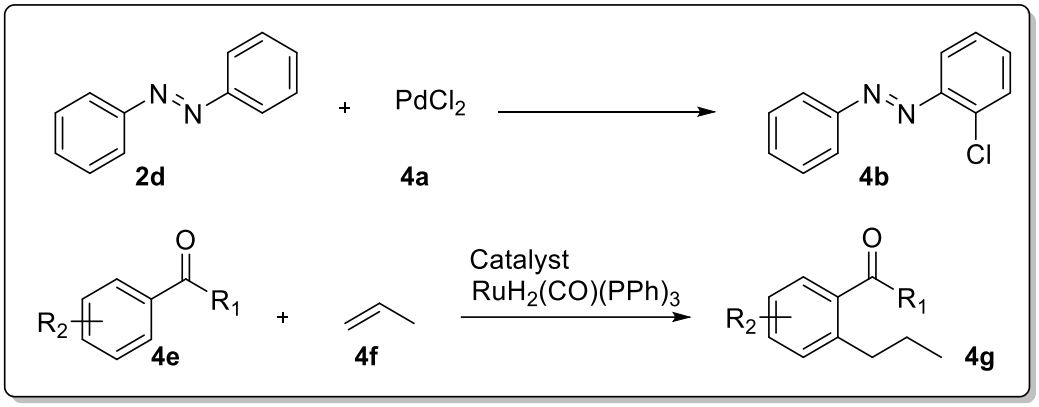
Scheme 2: Murahashi's report on cobalt catalyzed CO insertion of aldimine and azobenzene.

In 1963, Kleiman and Dubeck showed that the *ortho* C-H bond of azobenzene can be activated to form cyclopentadienyl[*o*-(phenylazo)phenyl] nickel complex. In 1965, Chatt and Davidson revealed the first example of C-H functionalization of arene and the formation of the corresponding ruthenium complex.[6] (Scheme 3)



Scheme 3: Dubeck and Davidson's report on azobenzene and naphthalene respectively.

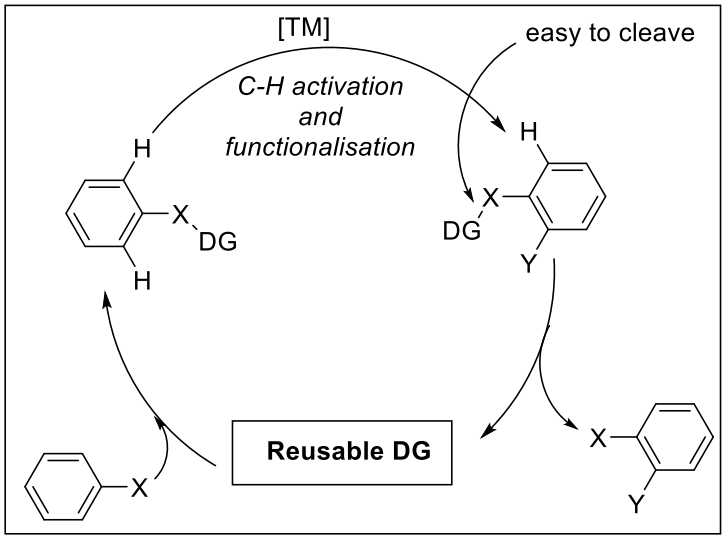
Successively, the chlorination of azobenzene using palladium as a catalyst is another example of C-H activation followed by functionalization, which was reported by Fahey in 1970. In 1993, an exciting report came from the Murai group, describing the C-H bond formation of aromatic ketone and olefin through the use of a ruthenium catalyst.[7,8] There has been rapid progress in the field of C-H activation for the last 20 years.



Scheme 4: Fahey's report on azobenzene using palladium catalyst (top), ruthenium catalyzed *ortho* functionalization of ketone reported by Murai (bottom).

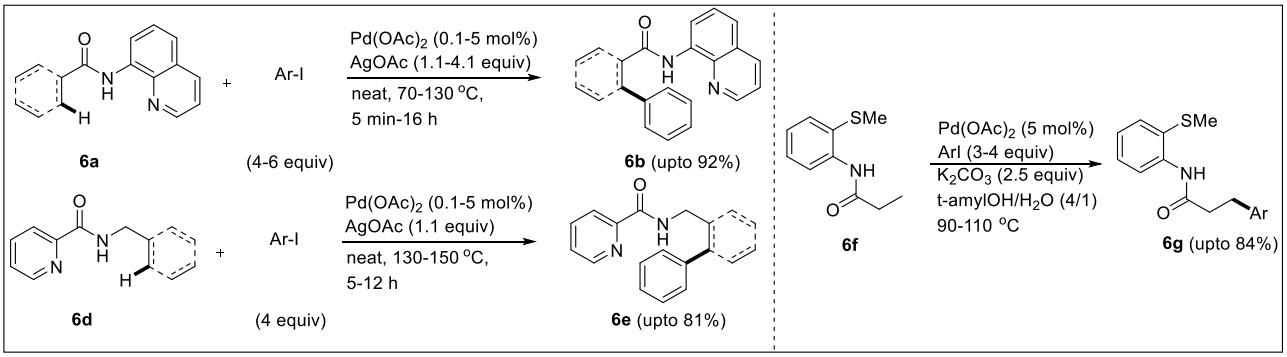
Directing group-assisted C-H activation reactions: There are some reports of direct sp^2(C)-H activation reactions. For example, in 2006, the Itami group reported direct C-H arylation of anisole with iodo benzene using rhodium as a catalyst with 51% overall yield (*p*/o: 71/29).[9] The directing group concept was then introduced to omit this issue. The capacity to bind the metal reversibly and control the regioselective activation of the C-H bond is provided by the directing groups, which are generally σ donors and have one or more heteroatoms or a rich *p*-electron cloud. As a result, the catalytic cycle was maintained by the directing groups' (DGs) ability to reversibly attach to metal. There are various types of DG reported in literature like non-modifiable, modifiable/ transformable, and/or reusable. A reusable directing group (DG)

can easily be installed in a substrate and recovered from C-H functionalized products. As a result, the C-H functionalization using reusable DG is both synthetically and economically practical.[4] (scheme 5)



Scheme 5: Reusable directing group assisted C-H functionalization.

In 2005, Daugulis introduced 8-aminoquinoline (**8AQ**) as a reusable directing group which directs the specific *ortho* C-H bond of arylamide to have the desired *ortho* arylated product. In the same report, they have described 2-picolinic acid as a directing group when linked with benzylamine substrate to have *ortho* C-H arylated product of benzylamine. They have also shown the *β*-selective arylated product of aliphatic carboxamide using 8-aminoquinoline as the directing group, and the *γ*-selective arylated product of aliphatic amine using 2-picolinic acid (**PA**) as the directing group. In 2010, another directing group 2-methylthio aniline (**SMe**) was also introduced by the Daugulis group. (scheme 6)



Scheme 6: Daugulis's work on the Pd(II)-catalyzed bidentate directing group-assisted C-H arylation.

Over the years, several directing groups have been introduced. Sanford reported *O*-acetyl oxime as a directing group for acetoxylation of both sp^2 and sp^3 C-H bonds with $Pd(OAc)_2$ and $PhI(OAc)_2$ in the presence of $AcOH/Ac_2O$.[10] Yu group demonstrated palladium-catalyzed

β-C(sp^3)-H arylated product of aliphatic carboxylic acid using 2,3,4,5,6-pentafluoroaniline as a removable directing group. In 2012, Sahoo and co-workers introduced *S*-methyl-*S*-2-pyridyl-sulfoximine (**MPyS**) as reusable directing for sp^2 C-H acetoxylation of benzoic acid, a direct and elegant approach for the *ortho* hydroxylation of benzoic acid. In 2016, Babu's group introduced 4-amino-2,1,3-benzothiadiazole (**ABTD**) as a re-usable directing group for Pd(II)-catalyzed arylation/oxygenation of β-C(sp^3/sp^2)-H bonds of carboxamides. A list of different directing groups[11] (mostly reusable) has been shown in Figures 1 and 2.

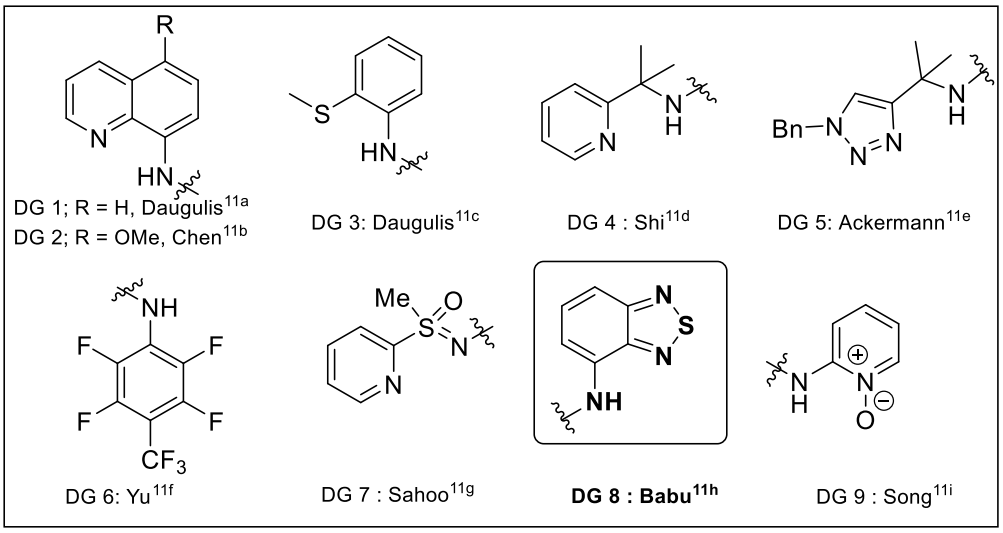


Figure 1: List of directing groups with -NH_2 functionality, where DG represents the directing group.

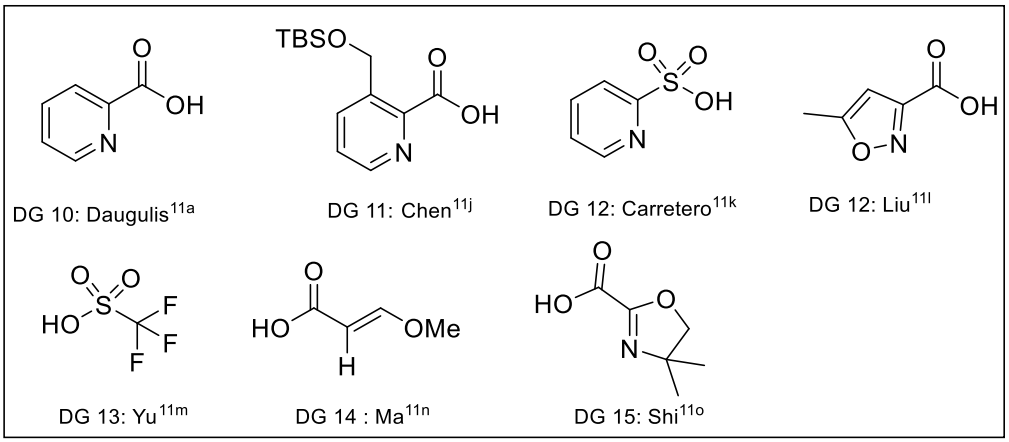
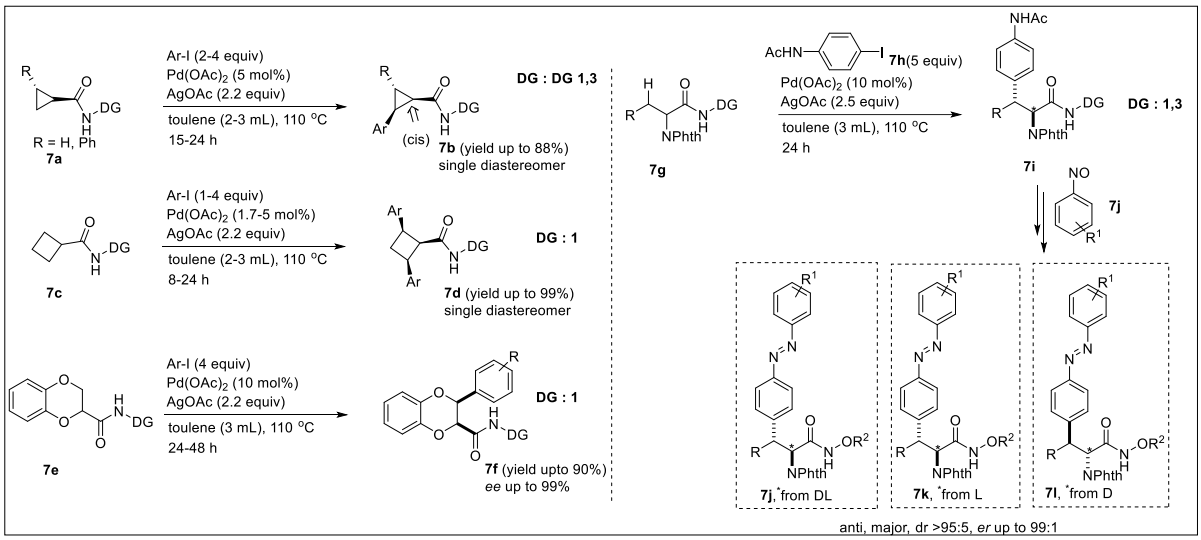


Figure 2: List of directing groups with –CO_2H functionality.

- **Our group contribution towards directing group assisted C-H functionalization**

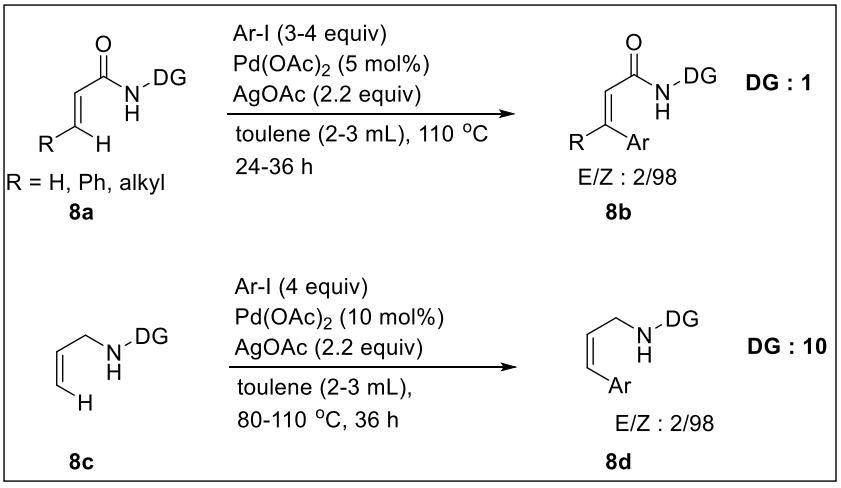
Before the introduction of the new directing group, our group has reported some outstanding work regarding β-C(sp^3)-H bond activation with high diastereoselectivity. In 2013, our group reported the synthesis of di- and tri-substituted cyclopropane carboxamides using palladium catalyst.[12a] Bis-arylation of cyclobutane carboxamides with high diastereoselectivity was described by our group in 2013.[12b] In 2015, palladium catalyzed direct arylation of C(sp^3)-H bonds of tetrahydrofuran and 1,4-benzodioxane systems with stereo as well as regioselectivity

were reported.[12c] Recently we have reported azobenzene-based unnatural amino acid *via* palladium catalyzed *β*-C(sp^3)-H functionalization strategy.[12d] (Scheme 7)



Scheme 7: Our group contribution towards *β*-C(sp^3)-H functionalization.

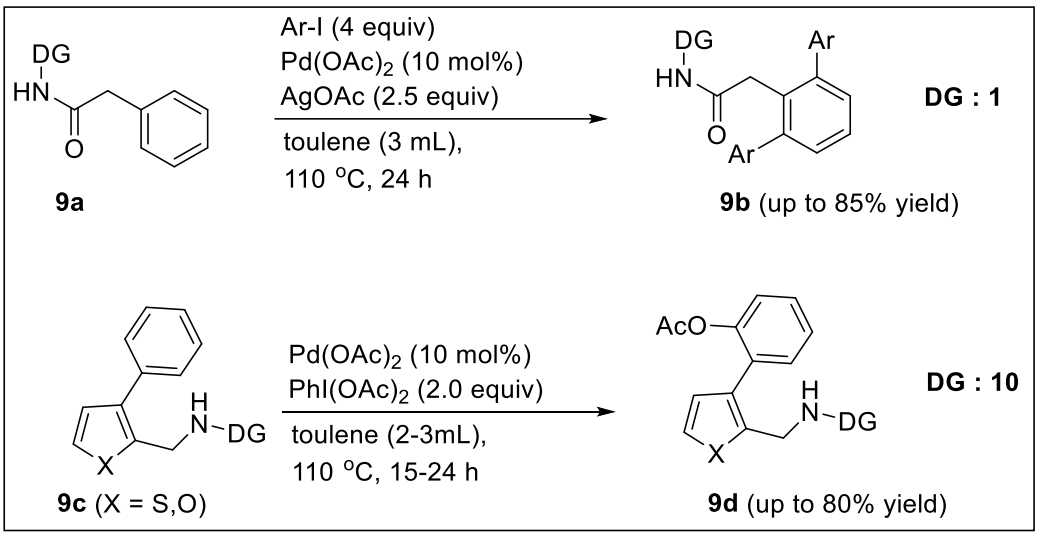
Babu's group also significantly contributed in the field of *β* and *γ*-C(sp^2)-H functionalization using palladium catalyzed C-H activation strategy. Z selective direct *β*-arylation of acrylamide systems and stereoselective synthesis of Z-cinnamamide scaffolds were reported using $Pd(OAc)_2$ as catalyst and AgOAc as additive.[12e] In 2017, our group reported the Z-selective *γ*-arylation of allylamines to construct Z-cinnamylamines using picolinic acid as the directing group. [13a] (Scheme 8)



Scheme 8: Report from our group on acrylamide and allylamine substrate.

Palladium catalyzed *γ*-C(sp^2)-H bis arylation/benzylation of the phenylacetic acid substrate using 8-aminoquinoline as a directing group was demonstrated by our group.[12f] In 2017, we demonstrated directing group-assisted remote *ε*-C(sp^2)-H mono acetoxylation in a hetero aryl-

aryl biaryl system.[13b] After functionalization, the directing group were uninstalled for every case using acid/base hydrolysis or esterification methods. (Scheme 9)

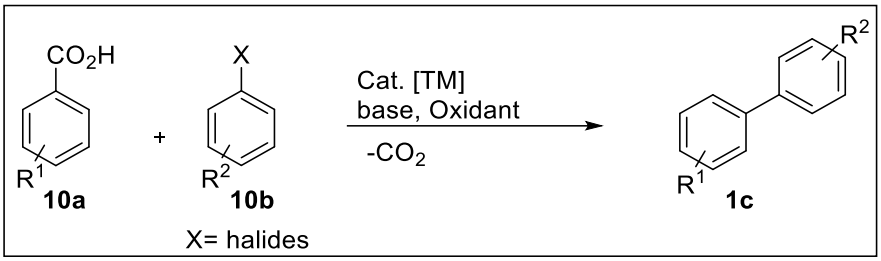


Scheme 9: γ-C(sp^2)-H arylation of arylacetic acid and ε-C(sp^2)-H acetoxylation of heteroaryl-biaryl scaffolds.

- **Literature based on synthesis of biaryl moieties using C-H activation methods**

Since the discovery of conducting polyacetylenes,[14] π-conjugated polymers like poly-*p*-phenylenes[15] have become field of interest for the scientific community owing their fine applications in the field of molecular electronics and nanotechnology.[16] Poly-phenylenes (PPn) is one of the important functional materials because of the high conductivity it shows when doped with either n- or p-type dopants.[17] It is a very useful material for obtaing organic light-emitting diodes[18] and ultraviolet laser dyes.[19] It acts as a connector between electron donor (D)-bridge (B)- electron acceptor (A) (i.e., D-B-A) in molecular assembly.[20] If we look into the structure of poly-*p*-phenylenes (PPn), we can see that it consists of a number of biaryl moieties. Biaryls themselves have been known to show antiamoebic, antifungal, anti-infective, antihypercholesteremic, antihyperlipoproteinemic, fasciolicide, antirheumatic, analgesic, anti-inflammatory, antithrombotic, uricosuric and antiarrhythmic properties.[21] When aromatic moieties bind with protein the hydrophobic character automatically increases and biaryls can easily interact with polar substituents and with positively charged substituents.[22] Because of their versatile nature biaryl compounds are very common in the pharmaceutical industry.

There are plenty of methods available to synthesize biaryl moieties. Ullmann synthesis[23] for symmetrical biaryls, Suzuki[24], Stille[25] and Negishi[26] cross-coupling and reaction involving organo silicates[27] for unsymmetrical biaryl are very well known in the literature. One of the important methods for the synthesis of biaryl is decarboxylative coupling reactions initiating from aryl carboxylic acid and aryl halide to form C-C bonds[28]. (Scheme 10)



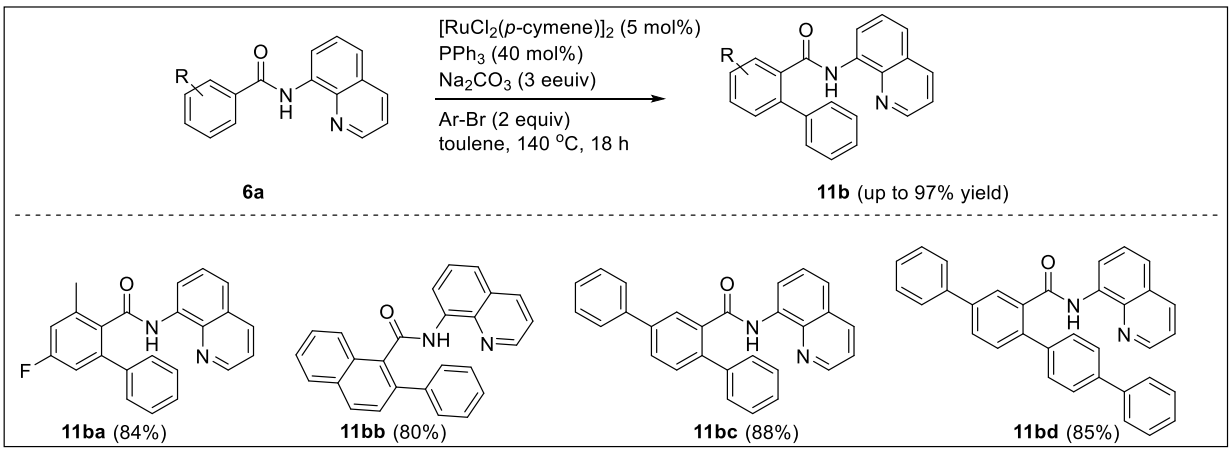
Scheme 10: Decarboxylative C-C cross-coupling reaction.

Recently transition metal catalyzed directing group assisted C-H arylation strategy is one of the finest ways to achieve biaryl precursor. Pre-functionalization issues can be easily avoided here and regioselectivity can also be introduced by using the right directing group. Here we will discuss some of the literature regarding directing group-assisted C(sp^2)-H functionalization to synthesize biphenyl, terphenyl, quaterphenyl, etc. using C-H activation as the key step.

- **Reusable directing group assisted C-H functionalization reactions for the synthesis of biaryl moiety**

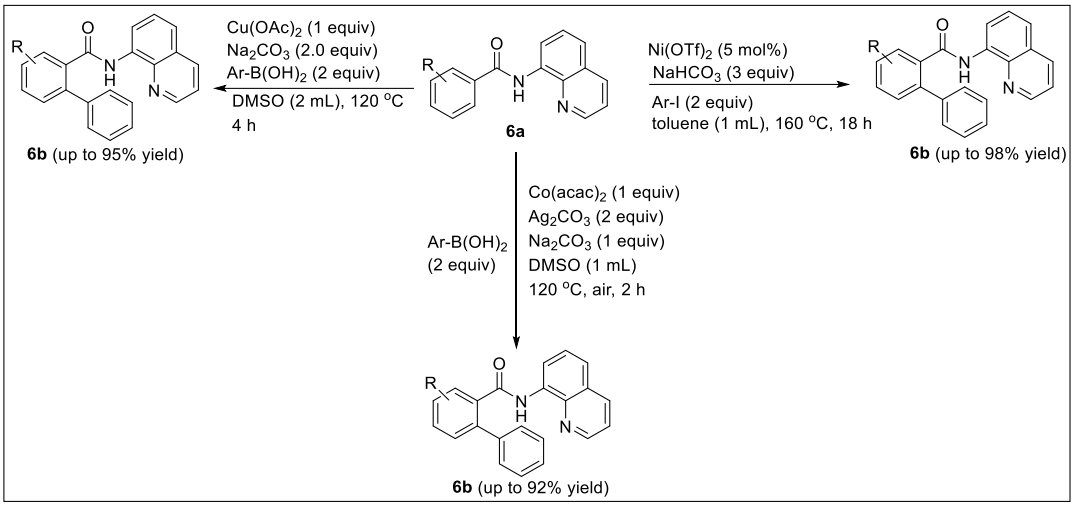
In 2005, the Daugulis[29a] group demonstrated the use of 8-aminoquinoline as a directing group for the formation of β arylated carboxamide using palladium (II) acetate as a catalyst, and AgOAc as an additive at 16 h in neat condition. In the same report they showed picolinic acid as the directing group for the synthesis of γ arylated amine. (Scheme 6)

Chatani[29b,c] group reported two works regarding β-C(sp^2)-H arylation of carboxamide using 8-aminoquinoline as directing group using ruthenium (Scheme 11) and nickel (Scheme 12) catalysis successively in 2013 and 2014. In that report, they showed various substituted biaryl compounds as well as terphenyl, quaterphenyl compounds. Effects of directing group have been described and they have used aryl bromide as the coupling partner here.



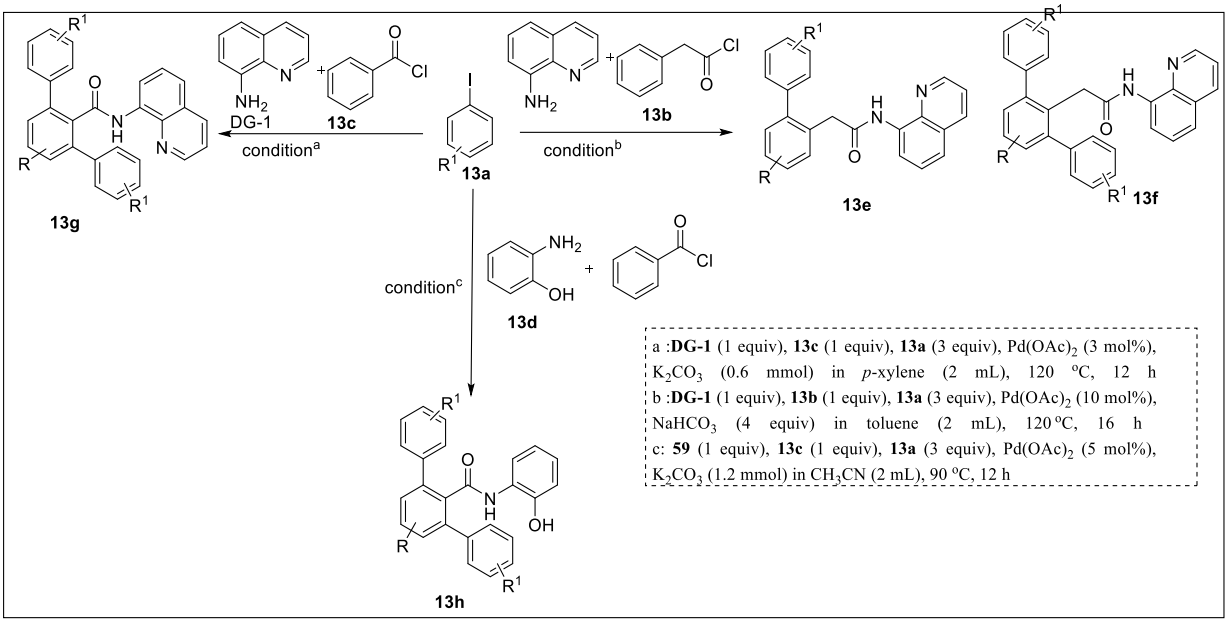
Scheme 11: Ruthenium catalyzed direct β-C(sp^2)-H arylation.

Nickel(II) catalyzed direct β-C(sp^2)-H arylation was developed by the Chatani group in 2014 using $Ni(OTf)_2$ as a catalyst in the presence of $NaHCO_3$ in toluene at 160 ^oC for 20 h. In 2016, copper catalyzed *o*-arylation of benzamide with arylboronic acid was reported by Tan[29d,e] group. In the same year, Cobalt promoted selective arylation of benzamide was also published by the same group. They have used aryl boronic acid as the coupling partner in this report as well. They have shown substituted biphenyl compounds and terphenyl compounds in both the reports. (Scheme 12)



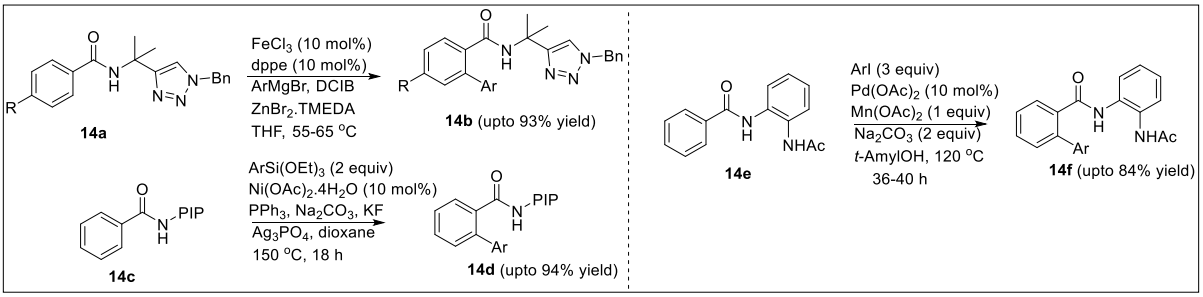
Scheme 12: Reports on nickel, copper, and cobalt catalyzed β-C(sp^2)-H arylation.

Step-economical one pot C-H activation is another profitable way to get the desired product. In most of the cases, free amine, acid chloride, and the coupling partner are added in the same pot and subjected to reaction conditions, which led to **50** as the desired product. Wan[30a,b,c] group first showed step economical one pot C-H activation method to synthesise *o*-aryl benzamides *via in situ* installation of directing group. For this reaction they heated the mixture of 8-amino quinoline, acid chloride, aryl iodide, palladium acetate, potassium carbonate using *p*-xylene at 130 ^oC for 12 h in one pot, *o*-arylated benzamide product is formed with 85% yield. In another report, they used the same directing group to get mono and bis-γ-C(sp^2)-H arylated phenylacetamides by palladium catalyzed C-H activation reaction in one pot manner. In 2017, they described multicomponent synthesis of various *o*-arylated benzamides using *o*-aminophenol as a directing group. (Scheme 13)



Scheme 13: Multicomponent one pot *β*-C(sp^2)-H arylation.

Apart from 8-aminoqunioline, there are reports on other directing groups also. In 2014, Ackermann[31a] introduced 2-(1-benzyl-1*H*-1,2,3-triazol-4-yl)propan-2-amine (TAM) as directing group. They used $FeCl_3$ as the catalyst and PhMgBr as the coupling partner. Similarly, Shi[31b] used 2-(pyridin-2-yl)isopropyl (PIP) amine as an effective directing group for synthesis of *o*-arylated benzamides. In this report, triethoxyarylsilane has been used as a coupling partner in the presence of $Ni(OAc)_2.4H_2O$ as the catalyst and PPh_3 as the ligand. Similar way, Watkins[31c] introduced *N*-(2-aminophenyl)acetamide as a directing group for the same using $Pd(OAc)_2$ as the catalyst. (Scheme 14)

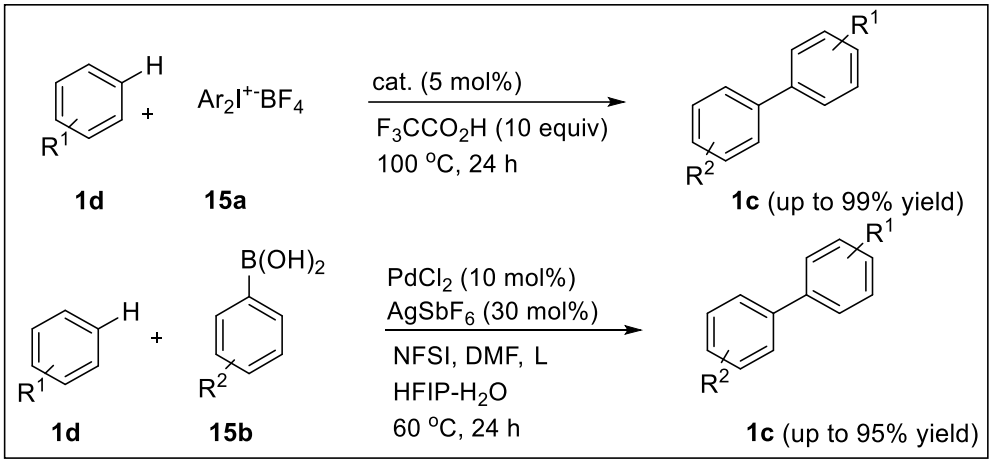


Scheme 14: Reports on TAM, PIP and APA directed *β*-C(sp^2)-H arylation.

- **Biaryl motifs using direct C-H activation methods**

Numerous reports available on synthesis of polyaryl compounds using direct C-H activation methods[32] without utilizing directing groups. Regioselectivty issue was overcome with electronic as well as steric effect. Greaney et al.[33a] reported Pd-catalyzed cross-coupling

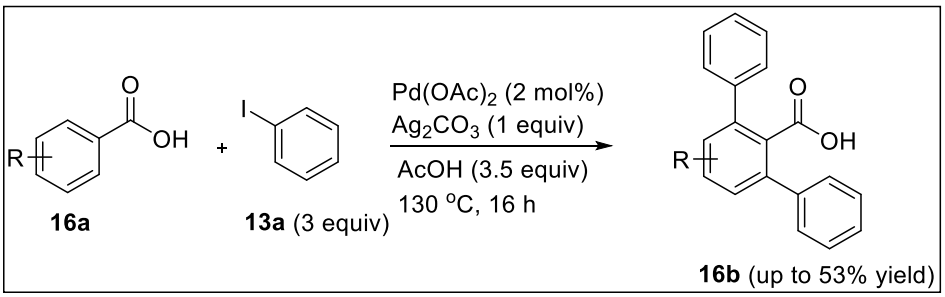
reactions between unactivated arenes and iodonium salts, affording the biaryls in high yields (up to 99%) without incorporating any directing groups. In 2017, Ye[33b] demonstrated *para*-selective arylation of simple arene controlled by amide using boronic acid as the coupling partner. (Scheme 15)



Scheme 15: Examples of direct C-H activation reactions for biaryl synthesis.

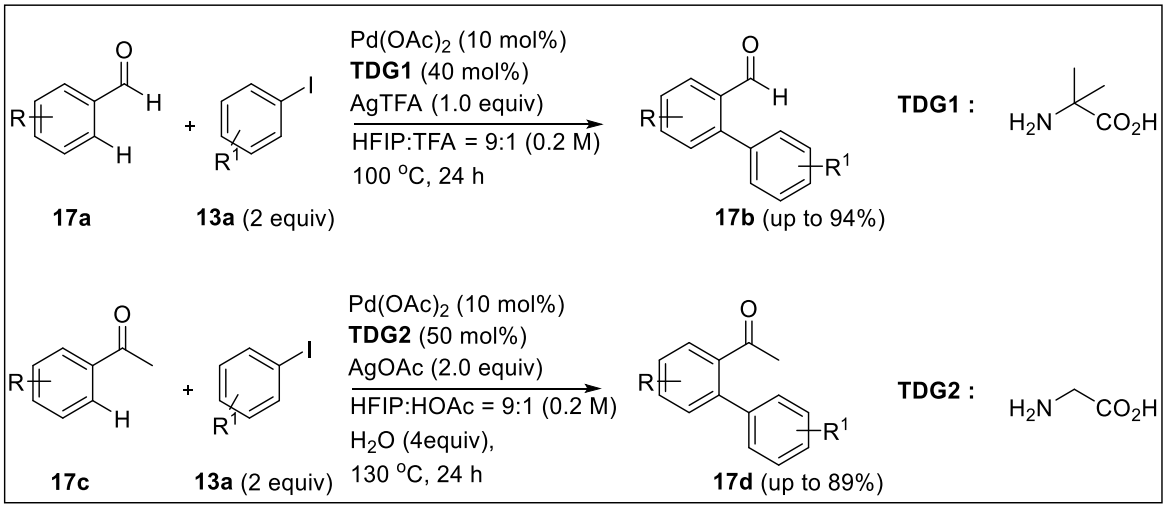
- **Synthesis of Biaryl motifs using acid and TDG directed C-H activation methods**

Acid directed C-H activation for the synthesis of substituted biaryl scaffolds is also well known in the literature. Daugulis and co-workers[34a] first reported *ortho*-arylation of benzoic acids using aryl halides. (Scheme 16) Following that, numerous reports have been added into literature[35].



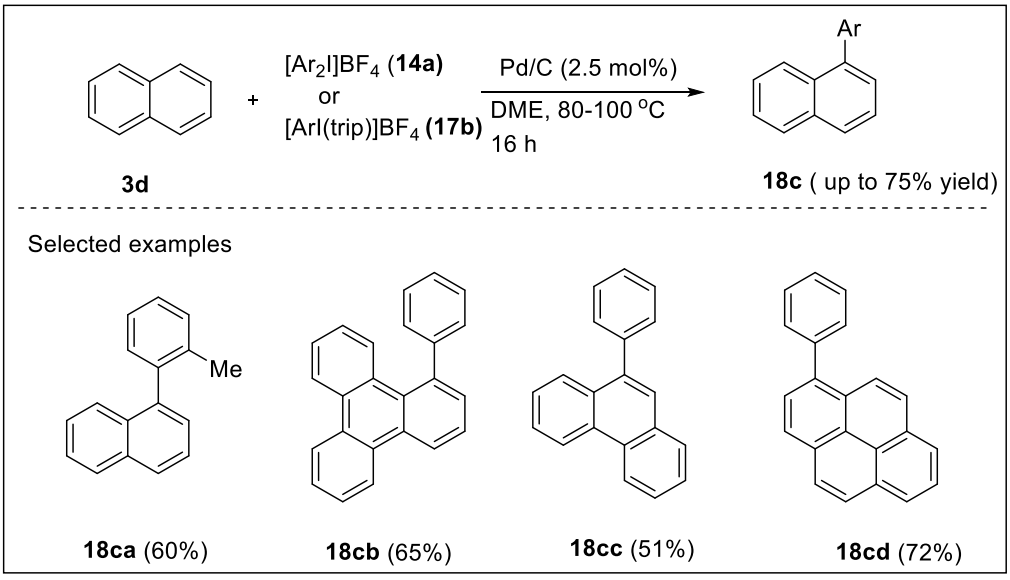
Scheme 16: Acid-directed C-H arylation reaction.

Transient directing group (TDG)[36a,b] mediated C-H activation methods for biaryl synthesis were developed in recent years. In that case directing group has been installed *in situ* in the reaction mixture and its removed from the substrate after C-H functionalization happened. It reduces the number of steps needed for directing group assisted C-H functionalization. In 2017, Yu et al. developed *β*-C(sp^2)-H arylation of benzaldehyde using transient directing groups. In this report, various proteinogenic and non-proteinogenic amino acids as transient directing groups were used, (Scheme 17) where 2-aminoisobutyric acid has shown the highest yield.



Scheme 17: *β*-C(sp^2)-H arylation of aldehyde and ketone using transient directing group.

- **Arylation of Polyaromatic hydrocarbon (PAH)**

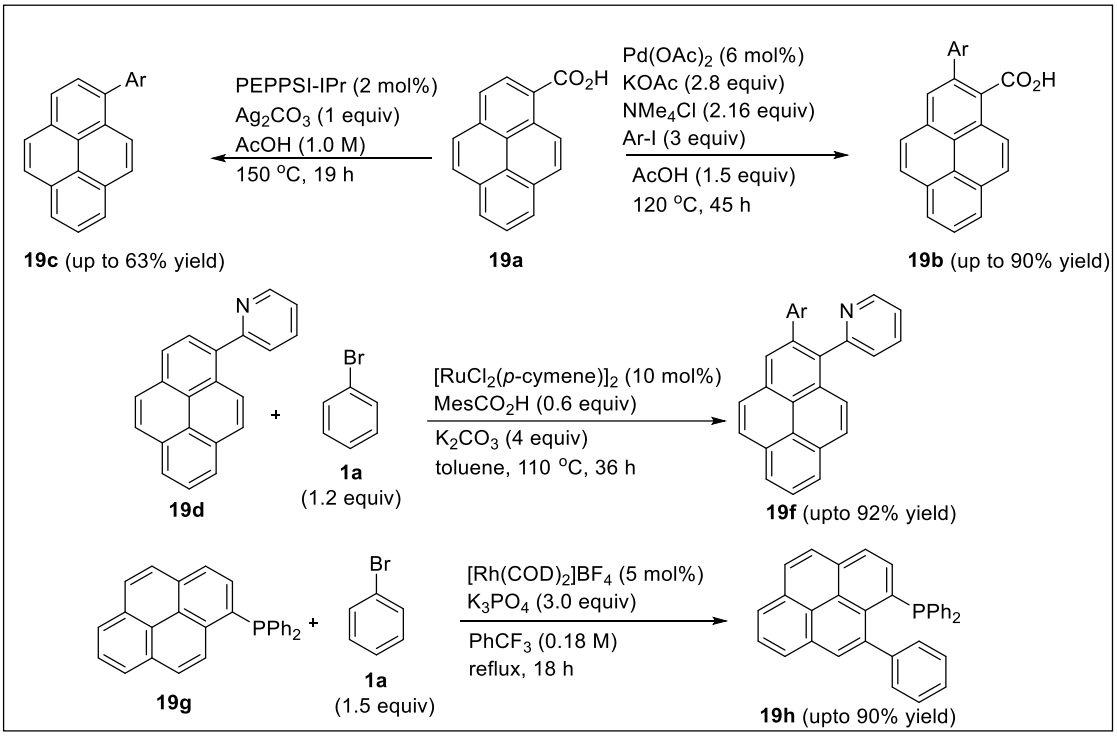


Scheme 18: Direct C-H arylation of polyaromatic compounds.

Arylation of Polyaromatic hydrocarbon (PAH) was also reported by using direct C-H activation methods. Polyaromatic hydrocarbons specially pyrene are well-known scaffolds in functional material because of their thermal stability as well as charge transfer property[37]. It is a challenging task to functionalize one specific position because of regioselectivity issue, several results have been established based on electronic and steric factors. Glorius[38] described selective arylation of polyaromatic hydrocarbon using Pd/C medium with aryl iodonium salt leading to biaryl products. (Scheme 18)

Acid-directed arylation of 1-pyrene carboxylic acid was reported by the Larossa[39a] group in 2020. In the same report, 2-aryl decarboxylated pyrene was also reported. Zhong[39b] group

demonstrated 2-pyridyl group assisted C2 arylation in pyrene moity and Roger[39c] group described phosphorus-directed rhodium-catalyzed C−H Arylation of 1-pyrenylphosphines Selective at the *K*-region. (Scheme 19)



Scheme 19: C-H arylation of pyrene scaffolds.

Recently, synthesis of biaryl unnatural amino acid derivatives (both racemic and enantiopure) using palladium catalysed *β*-C(sp^3)-H activation methodology with iodobiaryls has been disclosed by our group.[40]

Apart from this, cross-dehydrogenative coupling is a well-known way to synthesize biaryl as well as polyaryl scaffolds. In recent past metal free C-C coupling using non-metal catalyst such as bis(trifuoromethanesulfonyl)imide (HTFSI), *p*-toluenesulfonhydrazide (PTSH), P5a, 1,10-phenanthroline, eosin Y, and montmorillonite K-10 is another efficient way to get biarylated compounds.[41]

References:

1. (a) Jacques, J. *Revue d'histoire des sciences et de leurs applications* **1950**, 32-66. (b) Crabtree, R. H. *Chem. Rev*. **1985**, *85*, 245. (c) Shilov, A. E.; Shul'pin, G. B. *Chem. Rev*. **1997**, *97*, 2879. (d) Stahl, S. S.; Labinger, J. A.; Bercaw, J. E. *Angew. Chem. Int. Ed*. **1998**, *37*, 2180.

(e) Dyker, G. *Angew. Chem. Int. Ed*. **1999**, *38*, 1698. (f) Bergman, R. G. *Nature* **2007**, *446*, 391. (g) Lewis, J. R.; Bergman, R. G.; Ellman, J. A. *Acc. Chem. Res*. **2008**, *41*, 1013. (h) Chen, X.; Engle, K. M.; Wang, D. H.; Yu, J. Q. *Angew. Chem. Int. Ed.* **2009**, *48*, 5094. (i) Neufeldt, S. R.; Sanford, M. S. *Acc. Chem. Res*. **2012**, *45*, 936. (j) Kuhl, N.; Hopkinson, M. N.; Delord, J. W.; Glorius, F. *Angew. Chem. Int. Ed*. **2012**, *51*, 10236. (k) Arockiam, P. B.; Bruneau, C.; Dixneuf, P. H. *Chem. Rev*. **2012**, *112*, 5879. (l) Yeung, C. S.; Dong, V. M. *Chem. Rev*. **2011**, *111*, 1215. (m) Sun, C. L.; Li, B. J.; Shi, Z. J. *Chem. Rev*. **2011**, *111*, 1293. (n) Boorman, T.; Larrosa, I. *Chem. Soc. Rev*. **2011**, *40*, 1910. (o) Delord, J. W.; DrÖge, T.; Liu, F.; Glorius, F. *Chem. Soc. Rev.* **2011**, *40*, 4740. (p) Baudoin, O. *Chem. Soc. Rev.* **2011**, *40*, 4902. (q) Newhouse, T.; Baran, P. S. *Angew. Chem. Int. Ed*. **2011**, *50*, 3362. (r) Mkhalid, I. A. I.; Barnard, J. H.; Marder, T. B.; Murphy, J. M.; Hartwig, J. F. *Chem. Rev*. **2010**, *110*, 890. (s) Lyons, T. W.; Sanford, M. S. *Chem. Rev*. **2010**, *110*, 1147. (t) Jazzar, R.; Hitce, J.; Renaudat, A.; Sofack-Kreutzer, J.; Baudoin, O. *Chem.–Eur. J*. **2010**, *16*, 2654.

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

3. For selected reviews on Cross-coupling reaction, see: (a) Stille, J. K. *Angew. Chem. Int. Ed.* **1986**, *25*, 508. (b) Heck, R. F. *In Comprehensive Organic Synthesis, Vol. 4* (Eds.: Trost, B. M.; Fleming, I.), Pergamon, Oxford, **1991**, *833*. (c) Miyaura, N.; Suzuki, A. *Chem. Rev.* **1995**, *95*, 2457. (d) Hiyama, T. *J. Organomet. Chem*. **2002**, *653*, 58. (e) Negishi, E.-I.; Hu, Q.; Huang, Z.; Qian, M.; Wang, G. *Aldrichimica Acta* **2005**, *38*, 71. (f) Surry, D. S.; Buchwald, S. L. *Angew. Chem. Int. Ed*. **2008**, *47*, 6338. (g) Hartwig, J. F. *Nature* **2008**, *455*, 314. (h) Denmark, S. E.; Regens, C. S. *Acc. Chem. Res.* **2008**, *41*, 1486. (i) Hartwig, J. F. *Acc. Chem. Res*. **1998**, *31*, 852. (j) Wolfe, J. P.; Wagaw, S.; Marcoux, J. F.; Buchwald, S. L. *Acc. Chem. Res*., **1998**, *31*, 805.

4. For selected reviews on C-H activation chemistry, see: (a) Crabtree, R. H. *Chem. Rev*. **1985**, *85*, 245. (b) Kakiuchi, F.; Murai, S. *Acc. Chem. Res*., **2002**, *35*, 826. (c) Bergman, R. G. *Nature* **2007**, *446*, 391 (d) Chen, X.; Engle, K. M.; Wang, D. H.; Yu, J.-Q. *Angew. Chem. Int. Ed*. **2009**, *48*, 5094. (e) Mkhalid, I. A. I.; Barnard, J. H.; Marder, T. B.; Murphy, J. M.; Hartwig, J. F. *Chem. Rev*. **2010**, *110*, 890. (f) Lyons, T. W.; Sanford, M. S. *Chem. Rev*. **2010**, *110*, 1147. (g) Sun, C. L.; Li, B. J.; Shi, Z. J. *Chem. Rev*. **2011**, *111*, 1293. (h) Newhouse, T.; Baran, P. S. *Angew. Chem. Int. Ed*. **2011**, *50*, 3362 (i) Neufeldt, S. R.; Sanford, M. S. *Acc. Chem. Res*. **2012**, *45*, 936. (j) Kuhl, N.; Hopkinson, M. N.; Delord, J. W.; Glorius, F. *Angew. Chem. Int. Ed*. **2012**,

51, 10236. (k) Rouquet, G.; Chatani, N. *Angew. Chem. Int. Ed*. **2013**, *52*, 11726. (l) Daugulis, O.; Roane, J.; Tran, L. D. *Acc. Chem. Res*. **2015**, *48*, 1053. (m) Rit, R. K.; Yadav, M. R.; Ghosh, K.; Sahoo, A. K. *Tetrahedron* **2015**, *71*, 4450. (n) Castro, L. C. M.; Chatani, N. *Chem. Lett*. **2015**, *44*, 410. (o) Yang, X.; Shan, G.; Wang, L.; Rao, Y. *Tetrahedron Lett.* **2016**, *57*, 819. (p) He, J.; Wasa, M.; Chan, K. S. L.; Shao, Q.; Yu, J.-Q. *Chem. Rev*. **2017**, *117*, 8754. (q) Dalton, T.; Faber, T.; Glorius, F. *ACS Cent. Sci*. **2021**, *7*, 245. (r) Saini, G.; Kapur, M. *Chem. Commun*. **2021**, *57*, 1693. (s) Rej, S.; Ano, Y.; Chatani, N. *Chem. Rev*. **2020**, *120*, 1788. (t) Babu, S. A.; Aggarwal, Y.; Patel, P.; Tomar, R. *Chem. Commun.* **2022**, *58*, 2162. (u) Babu, S. A.; Dalal, A.; Bodak, S. *Chemistry* **2023**, *5*, 2713.

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

6. (a) Kleiman, J. P.; Dubeck, M. *J. Am. Chem. Soc*. **1963**, *85*, 1544. (b) Chatt, J.; Davidson, J. M. *J. Chem. Soc*. **1965**, 843.

7. (a) Fahey, D. R. *J. Organomet. Chem*. **1971**, *27*, 283. (b) Fahey, D. R. *J. Chem. Soc. D* **1970**, 417a.

8. Murai, S.; Kakiuchi, F.; Sekine, S.; Tanaka, Y.; Kamatani, A.; Sonoda, M.; Chatani, N. *Nature* **1993**, *366*, 529.

9. Yanagisawa, S.; Sudo, T.; Noyori, R.; Itami, K. *J. Am. Chem. Soc.* **2006**, *128*, 11748.

10. Neufeldt, S. R.; Sanford, M. S. *Org. Lett*., **2010**, *12*, 532.

11. (a) Zaitsev, V. G.; Shabashov, D.; Daugulis, O. *J. Am. Chem. Soc*. **2005**, *127*, 13154. (b) He, G.; Zhang, S.-Y.; Nack, W. A.; Li, Q.; Chen, G. *Angew. Chem. Int. Ed*. **2013**, *52*, 11124. (c) Shabashov, D.; Daugulis, O. *J. Am. Chem. Soc*. **2010**, *132*, 3965. (d) Zhang, Q.; Chen, K.; Rao, W.; Zhang, Y.; Chen, F. J.; Shi, B. F. *Angew. Chem., Int. Ed*. **2013**, *52*, 13588. (e) Gu, Q.; Al Mamari, H. H.; Graczyk, K.; Diers, E.; Ackermann, L. *Angew. Chem. Int. Ed.* **2014**, *53*, 3868. (f) Chan, K. S. L.; Wasa, M.; Wang, X.; Yu, J.-Q. *Angew. Chem. Int. Ed.* **2011**, *50*, 9081. (g) Rit, R. K.; Yadav, M. R.; Sahoo, A. K. *Org. Lett.* **2012**, *14*, 3724. (h) Reddy, C.; Bisht, N.; Parella, R.; Babu, S. A. *J. Org. Chem*. **2016**, *81*, 12143. (i) Zhang, S.-K.; Yang, X.-Y.; Zhao, X.-M.; Li, P.-X.; Niu, J.- L.; Song, M.-P. *Organometallics* **2015**, *34*, 4331. (j) He, G.; Chen, G. *Angew. Chem. Int. Ed*. **2011**, *50*, 5192. (k) Rodriguez, N.; Romero-Revilla, J. A.; Fernandez-Ibanez, M. A.; Carretero, J. C. *Chem. Sci*. **2013**, *4*, 175. (l) Pasunooti, K. K.; Banerjee, B.; Yap, T.; Jiang, Y.; Liu, C.-F. *Org. Lett*. **2015**, *17*, 6094. (m) Chan, K. S. L.; Wasa, M.; Chu, L.; Laforteza, B. N.; Miura, M.; Yu, J.-Q. *Nat. Chem.* **2014**, *6*, 146. (n) Fan, M.; Ma, D. *Angew. Chem., Int. Ed*. **2013**, *52*, 12152.

12. Selected paper from our group dealing with bidentate DG-aided C–H functionalization: (a) Parella, R.; Gopalakrishnan, B.; Babu, S. A. *Org. Lett*. **2013**, *15*, 3238. (b) Parella, R.; Gopalakrishnan, B.; Babu, S. A. *J. Org. Chem*. **2013**, *78*, 11911. (c) Parella, R.; Babu, S. A. *J. Org. Chem.* **2015**, *80*, 2339. (d) Tomar, R.; Suwasia, S.; Choudhury, A. R.; Venkataramani, S.; Babu, S. A. *Chem. Commun*. **2022**, *58*, 12967. (e) Parella, R.; Babu, S. A. *J. Org. Chem.* **2015**, *80*, 12379. (f) Bisht, N.; Babu, S. A. *Tetrahedron* **2016**, *72*, 5886.

13. Selected paper from our group dealing with bidentate DG-aided C–H functionalization: (a) Parella, R.; Babu, S. A. *J. Org. Chem.* **2015**, *82*, 6550. (b) Naveen; Rajkumar, V.; Babu, S. A.; Gopalakrishnan, B. *J. Org. Chem.* **2016**, *81*, 12197.

14. (a) Shirakawa, H.; Louis, E. J.; MacDiarmid, A. G.; Chiang, C. K.; Heeger, A. J. *Chem. Commun.* **1977**, *16*, 578–580. (b) MacDiarmid, A. G. *Angew. Chem., Int. Ed*. **2001**, *40*, 2581–2590.

15. (a) Wallow, T. I.; Novak, B. N. *J. Am. Chem. Soc.* **1991**, *113*, 7411. (b) Gin, D. G.; Conticello, V. P.; Grubbs, R. H. *J. Am. Chem. Soc*. **1992**, *114*, 3167. (c) Tour, J. M. *AdV. Mater*. **1994**, *6*, 190. (d) Berresheim, A. J.; Muller, M.; Mullen, K. *Chem. Rev*. **1999**, *99*, 1747. (d) Banerjee, M., Shukla, R., Rathore, R. *J. Am. Chem. Soc*. **2009**, *131*, 1780.

16. (a) *Introduction to Molecular Electronics*, Petty, M. C., Bryce, M. R., Bloor, D., Eds.; Oxford Univ. Press: New York, **1995**. (b) Gross, M.; Muller, D. C.; Nothofer, H. -G.; Scherf, U.; Neher, D.; Brauchle., C.; Meerholz, K. *Nature* **2000**, *405*, 661. (c) Craig, M. R.; Kok, M. M. de; Hofstraat, J. W.; Schenning, A. P. H. J.; Meijer, E. W. *J. Mater. Chem*. **2003**, *13*, 2861. (d) *Organic Electronics*; Klauk, H., Ed.; Wiley-VCH: Weinheim, **2006**.

17. Shacklette, L. W.; Eckhardt, H.; Chance, R. R.; Miller, G. G.; Ivory, D. M.; Baughman, R. H. *J. Chem. Phys*. **1980**, *73*, 4098.

18. (a) Meghdadi, F.; Tasch, S.; Winkler, B.; Fischer, W.; Stelzer, F.; Leising, G. *Synth. Met*. **1997**, *85*, 1441. (b) Baur, J. W.; Kim, S.; Balanda, P. B.; Reynolds, J. R.; Rubner, M. F. *Adv. Mater*. **1998**, *10*, 1452.

19. Rinke, M.; Gusten., H; Ache, H. J. *J. Phys. Chem*. **1986**, *90*, 2666.

20. (a) Weiss, E. A.; Tauber, M. J.; Kelley, R. F.; Ahrens, M. J.; Ratner, M. A.; Wasielewski, M. R. *J. Am. Chem. Soc*. **2005**, *127*, 11842. (b) Plummer, E. A.; Hofstraat, J. W.; De Cola, L. *Dalton Trans*. **2003**, 2080. (c) Weiss, E. A.; Ahrens, M. J.; Sinks, L. E.; Gusev, A. V.; Ratner, M. A.; Wasielewski, M. R. *J. Am. Chem. Soc.* **2004**, *126*, 5577. (d) Welter, S.; Salluce, N.; Benetti, A.; Rot, N.; Belser, P.; Sonar, P.; Grimsdale, A. C.; Mullen, K.; Lutz, M.; Spek, A. L.; De Cola, L. *Inorg. Chem*. **2005**, *44*, 4706. (e) Schlicke, B.; Belser, P.; De Cola, L.; Sabbioni, E.; Balzani, V. *J. Am. Chem. Soc*. **1999**, *121*, 4207. (f) Sun, D.; Lindeman, S. V.; Rathore, R.;

Kochi, J. K. *J. Chem. Soc., Perkin Trans. 2* **2001**, 1585. (g) Ward, M. D. *Chem. Soc. Rev*. **1995**, 121. (h) Martin, R. E.; Diederich, F. *Angew. Chem., Int. Ed*. **1999**, *38*, 1350.

21. Bemis, G. W.; Murcko, M. A. *J. Med. Chem*. **1996**, *39*, 2887.

22. Hajduk, P. J.; Bures, M.; Praestgaard, J.; Fesik, S. W. *J. Med. Chem*. **2000**, *43*, 3443.

23. Ullmann, F. Ber. **1903**, *36*, 2389.

24. Sato, M.; Miyaura, N.; Suzuki, A. *Chem. Lett.* **1989**, 1405.

25. Labadie, J. W.; Tueting, D.; Stille, J. K. *J. Org. Chem*. **1983**, *48*, 4634.

26. Negishi, E.-I.; King, A. O.; Okukado, N. *J. Org. Chem*. **1977**, *42*, 1821.

27. Homsi, F.; Nozaki, K.; Hiyama, T. *Tetrahedron Lett*. **2000**, *41*, 5869.

28. Rodrıguez, N., Goossen, L. J, *Chem. Soc. Rev*., **2011**, *40*, 5030.

29. (a) Zaitsev, V. G.; Shabashov, D.; Daugulis, O. *J. Am. Chem. Soc*. **2005**, *127*, 13154. (b) Aihara, Y.; Chatani, N. *Chem. Sci*., **2013**, *4*, 664 (c) Aihara, Y.; Chatani, N. *J. Am. Chem. Soc*. **2014**, *136*, 898. (d) Hu, L.; Gui, Q.; Chen, X.; Tan, Z.; Zhu, G. *Org. Biomol. Chem*., **2016**, *14*, 11070.

30. (a) For one pot multicomponent β-C(sp^2)-H arylation, see: (a) Liu, Y.; Zhang, Y.; Huang, M.; Wan, J.-P. *RSC Adv*., **2015**, *5*, 46192. (b) Liu, Y.; Huang, B.; Cao, X.; Wan, J.-P. *ChemCatChem* **2016**, *8*, 1470. (C) Liu, Y.; Wan, J.-P. *J. Org. Chem*. **2017**, *82*, 8950.

31. For Different directing groups for β-C(sp^2)-H arylation, see: (a) Gu, Q.; Al Mamari, H. H.; Graczyk, K.; Diers, E.; Ackermann, L. *Angew. Chem., Int. Ed*. **2014**, *53*, 3868. (b) Zhao, S.; Liu, B.; Zhan, B.-B.; Zhang, W.-D.; Shi, B.-F. *Org. Lett*. **2016**, *18*, 4586. (c) Reddy, M. D.; Blanton, A. N.; Watkins, E. B. *J. Org. Chem*. **2017**, *82*, 5080.

32. For selective review on direct C-H bond activation (a) Kuhl, N.; Hopkinson, M. N.; Wencel-Delord, J.; Glorius, F. *Angew. Chem. Int. Ed*. **2012**, *51*, 10236. (b) Ackermann, L.; Vicente, R. *Top. Curr. Chem*. **2010**, *292*, 211. (c) Ackermann, L.; Vicente, R.; Kapdi, A. R. *Angew. Chem. Int. Ed*. **2009**, *48*, 9792. (d) Alberico, D.; Scott, M. E.; Lautens, M. *Chem. Rev.* **2007**, *107*, 174. (e) Miura, M.; Nomura, M. *Top. Curr. Chem*. **2002**, *219*, 211.

33. (a) Storr, T. E.; Greaney, M. F. *Org. Lett*. **2013**, *15*, 1410. (b) Luan, Y.-X.; Zhang, T.; Yao, W.-W.; Lu, K.; Kong, L.-Y.; Lin, Y.-T.; Ye, M. *J. Am. Chem. Soc*. **2017**, *139*, 1786.

34. Chiong, H. A.; Pham, Q.-N.; Daugulis, O. *J. Am. Chem. Soc*. **2007**, *129*, 9879.

35. Selected review on acid directed C-H arylation, see: (a) Font, M.; Quibell, J. M.; Perry, G. J. P.; Larrosa, I. *Chem. Commun*. **2017**, *53*, 5584. (b) Drapeau, M. P.; Gooßen, L. J. *Chem. - Eur. J*. **2016**, *22*, 18654.

36. (a) Liu, X.-H.; Park, H.; Hu, J.-H.; Hu, Y.; Zhang, Q.-L.; Wang, B.-L.; Sun, B.; Yeung, K.-S.; Zhang, F.-L.; Yu, J.-Q. *J. Am. Chem. Soc*. **2017**, *139*, 888. (b) Xu, J.; Liu, Y.; Wang, Y.; Li, Y.; Xu, X.; Jin, Z. *Org. Lett*. **2017**, *19*, 1562.

37. Selected reports dealing with polyaromatic hydrocarbon, see: (a) Wang, C.; Dong, H.; Hu, W.; Liu, Y.; Zhu, D. *Chem. Rev*. **2012**, *112*, 2208. (b) Sun, Z.; Ye, Q.; Chi, C.; Wu, J. *Chem. Soc. Rev*. **2012**, *41*, 7857. (c) Figueira-Duarte, T. M.; Müllen, K. *Chem. Rev*. **2011**, *111*, 7260. (d) Wu, J.; Pisula, W.; Müllen, K. *Chem. Rev*. **2007**, *107*, 718. (e) Anthony, J. E. *Chem. Rev*. **2006**, *106*, 5028.

38. Collins, K. D.; Honeker, R.; Vasquez-´ Cespedes, S.; Tang, D.-T. D.; Glorius, F.´ *Chem. Sci*. **2015**, *6*, 1816.

39. (a) Just-Baringo, X.; Shin, Y.; Panigrahi, A.; Zarattini, M.; Nagyte, V.; Zhao, L.; Kostarelos, K.; Casiraghi, C.; Larrosa, I. *Chem. Sci*. **2020**, *11*, 2472. (b) He, Y.-Q.; Zhong, Y.-W. *Chem. Commun*. **2015**, *51*, 3411. (c) Sire, C.; Cattey, H.; Tsivery, A.; Hierso, J. -C.; Roger, J. *Adv. Synth. Catal*. **2022**, *364*, 440.

40. Banga, S.; Kaur, R.; Babu, S. A. *Eur. J. Org. Chem*. **2021**, 3641.

41. Yi, H.; Zhang, G.; Wang, H.; Huang, Z.; Wang, J.; Singh, A. K.; Lei, A. W. *Chem. Rev.* **2017**, *117*, 9016.

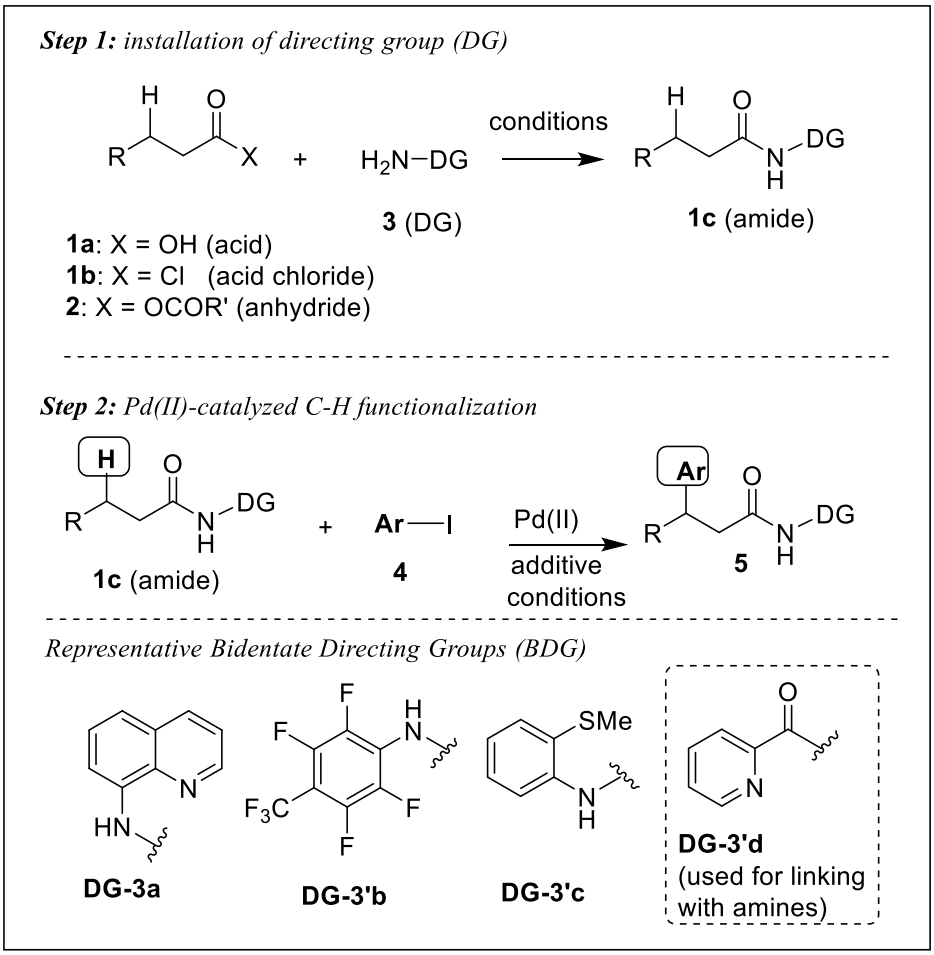
Chapter 2

One-pot, solvent-free Pd(II)-catalyzed direct *β*-C-H arylation of carboxamides involving anhydrides as substrates *via in situ* installation of directing group.

For the purpose of this Thesis work, the work of Chapter 2 is re-used (adapted) with permission from (Dalal A., Babu, S.A*., *Tetrahedron*, **2019**, *75*, pp 1246-1257. Title; One-pot, solvent-free Pd(II)-catalyzed direct *β*-C-H arylation of carboxamides involving anhydrides as substrates *via in situ* installation of directing group).

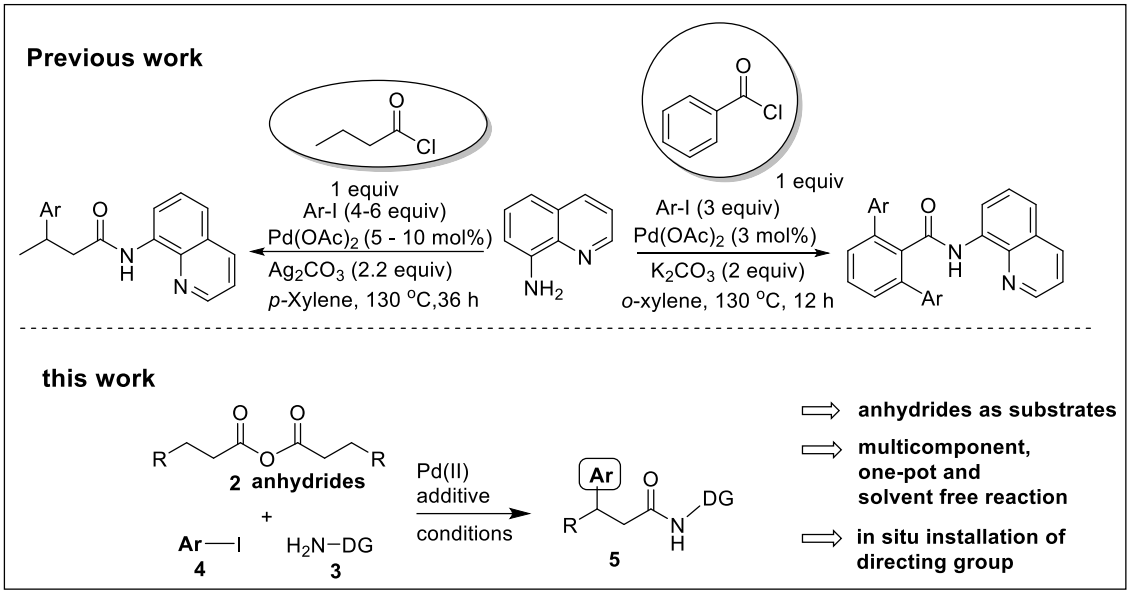
The sp^2/sp^3 C-H activation and C-C bond forming reactions catalyzed by the transition metal catalysts are considered pivotal organic transformations.[1] The site-selective functionalization of C-H bonds of small organic molecules with the assistance of directing groups (DGs) is one of the important tactics to obtain the corresponding functionalized small organic molecules.[1,2] Especially, the seminal paper[3a,b] by Daugulis et al., which revealed the bidentate DG 8-aminoquinoline (**DG-3a**, Scheme 1) assisted direct arylation of *β*-C(sp^2)–H bonds of benzamides and *β*-C(sp^3)–H bonds of aliphatic carboxamides has led to the development of dependable methods for obtaining various functionalized carboxamides.[3-7] Apart from 8-aminoquinoline (AQ), other DGs similar to AQ were also demonstrated for accomplishing the *β*-C–H functionalization of aromatic and aliphatic carboxylic acids.[2]

Even though the C-H functionalization of carboxamides with bidentate DG (such as 8-aminoquinoline) assistance is regarded as a crucial synthetic transformation, this procedure actually requires two steps[2,3,5-7]. A DG (for example, **DG-3a**) with an amine functionality is coupled with a carboxylic acid (**1a**) or its derivative, such as an acid chloride (**1b**), in the first step to produce the corresponding carboxamide (**1c**), which is installed with the **DG-3a**. In the following step, the carboxamide **1c** is then exposed to a Pd(II)-catalyzed, DG-assisted C-H activation/arylation in the presence of an additive (such as AgOAc, Ag_2CO_3, etc.) to produce the -C-H arylated carboxamide (**5**)[3a,b]. The literature is well-versed on the function of additives in $Pd(OAc)_2$-catalyzed C-H arylation processes, such as AgOAc or Ag_2CO_3.[2-7] In the proposed Pd^{II}-Pd^{IV} catalytic cycle, these additives serve as the I^- (iodide anion) scavenger to replenish the Pd(II)-catalyst.[2,3a,b]



Scheme 1. Steps involved in the typical Pd(II)-catalyzed C-H arylation of carboxamides.

The creation of the most perfect and simple multicomponent-based C-H activation techniques will be highly valued because it is step-economical[4d]. Along with this goal, it would be advantageous to make the bidentate DG-assisted Pd(II)-catalyzed C-H functionalization of carboxamide (e.g., **1c**), a simple procedure. Towards this, recently our group,[4a] Wan[4b] and Liu[4c] reported the Pd(II)-catalyzed C-H arylation of carboxamides *via* the multicomponent reaction comprising acid chlorides (**1b**), aryl iodides (**4**) and 8-aminoquinoline (**3a**) (Scheme 2). Although a simple Pd(II)-catalyzed C-H arylation of carboxamides was demonstrated using a multicomponent reaction including acid chlorides,[4] it should be emphasised that some acid chlorides require special handling and storage considerations. Thus, we envisaged to attempt the Pd(II)-catalyzed C-H arylation of carboxamides *via* the multicomponent reaction involving anhydrides as substrates (**2**) instead of acid chlorides (**1b**). In continuation of our work on the C-H activation/arylation reactions,[5] herein we report a multicomponent-type reaction comprising Pd(II)-catalyzed *β*-C-H arylation of carboxamides involving anhydrides as substrates (**2**) *via in situ* installation of bidentate DG under solvent free condition (Scheme 2).



Scheme 2. Multicomponent Pd(II)-catalyzed C-H arylation of carboxamides *via in situ* installation of directing group.

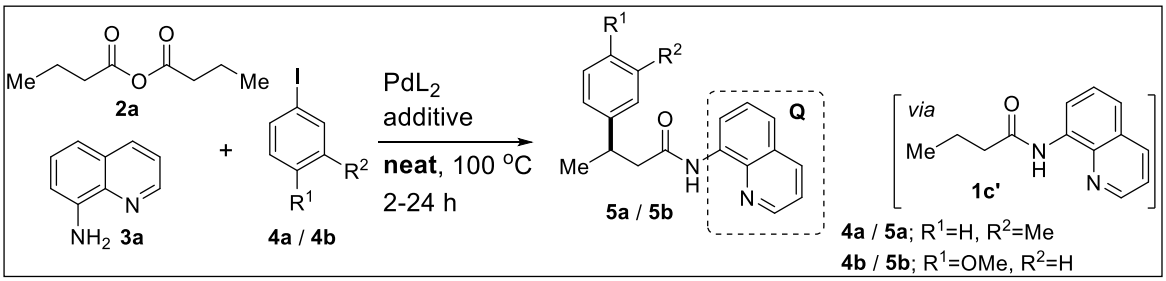
Results and Discussion

To begin the investigation on multicomponent-type Pd(II)-catalyzed *β*-C-H arylation of carboxamides involving anhydrides as substrates *via in situ* installation of DG, initially, we performed optimization reactions using butyric anhydride (**2a)** (Table 1). It is to be noted that typically the bidentate DG-assisted C-H arylation of carboxamides were performed using the Pd(II) catalyst and also an additive (e.g., AgOAc or Ag_2CO_3), which will act as the halide ion scavenger to regenerate the Pd(II)-catalyst.[2,3-5,7] At first, we heated a mixture of butyric anhydride (**2a**, 1 equiv), **DG-3a** (1 equiv), *m*-tolyl iodide (**4a**, 6 equiv) and $Pd(OAc)_2$ catalyst (10 mol%) in the absence of any additive at 110 °C for 24 h. This reaction did not afford the methylene *β*-C-H arylated product **5a** (entry 1, Table 1). The same reaction was performed in the presence of AgOAc as an additive without any Pd(II) catalyst. However, this reaction also did not afford the *β*-C-H arylated product **5a** (entry 2, Table 1). These reactions indicated that the absence of the $Pd(OAc)_2$ catalyst or additive AgOAc did not promote the C-H arylation reaction.

Subsequently, we heated a mixture of butyric anhydride (**2a**), 8-aminoquinoline, (**3a**), *m*-tolyl iodide (**4a**), $Pd(OAc)_2$ catalyst (10 mol%) and AgOAc (additive, 2.2 equiv) at 110 °C for 24 h. To our delight, this reaction afforded the expected methylene *β*-C-H arylated product **5a** in 94% yield. This multicomponent-type arylation reaction afforded the product **5a** *via* in situ formation of carboxamide **1c′** and installation of **DG-3a** under solvent free condition (entry 3, Table 1). Next, we performed the Pd(II)-catalyzed multicomponent-type arylation reaction

comprising anhydride **2a** (1 equiv), **3a** (1 equiv) and **4a** (6 equiv) using Ag_2CO_3 instead of AgOAc as an additive. This reaction also gave the product **5a** in 87% yield (entry 4, Table 1). Given that the reactions were performed without any solvent, the above trial reactions were done using 6 equiv of **4a** to have adequate homogeneousness. Notably, use of 4 or 5 equiv of **4a** also gave the product **5a** in appreciable yields (67 and 81%) (entries 5 and 6, Table 1).

Table 1. Optimization of the reaction conditions. One-pot Pd(II)-catalyzed direct *β*-C-H arylation of carboxamide **1c′** derived from butyric anhydride **2a**[a]



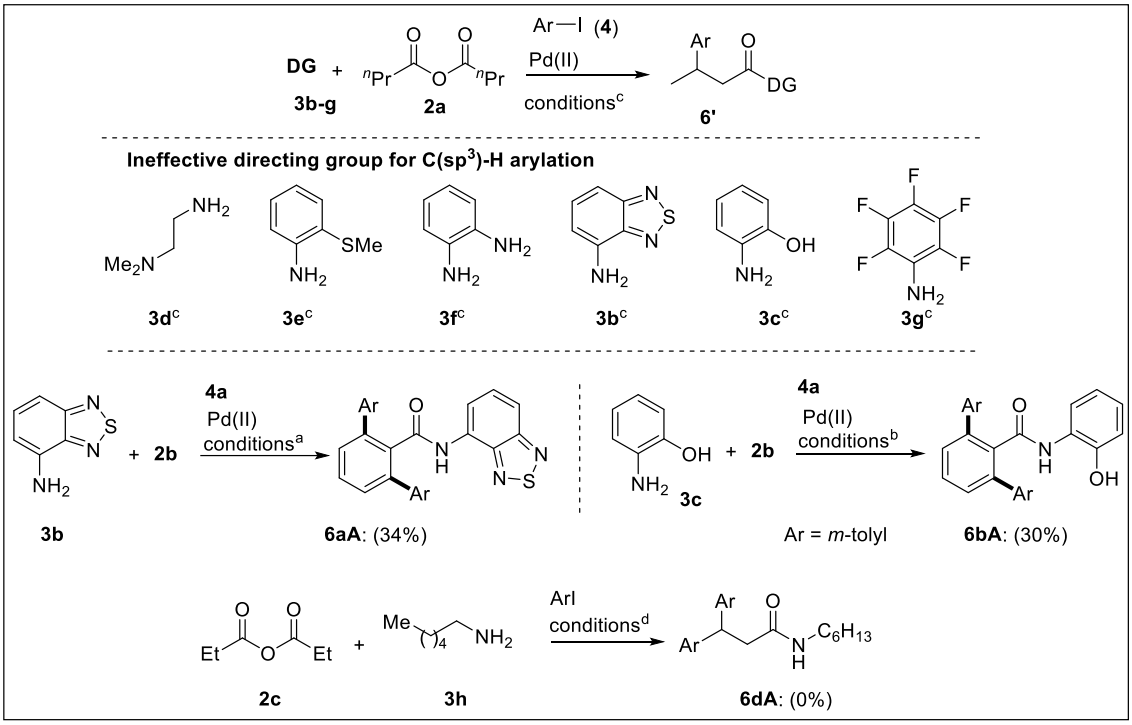
Entry	PdL_2 (x mol%)	4a: ArI (mmol)	Additive (1.1 mmol)	Time (h)	5a: yield (%)
1	$Pd(OAc)_2$ (10)	3	Nil	24	0
2	Nil	3	AgOAc	24	0
3	**$Pd(OAc)_2$ (10)**	**3**	**AgOAc**	**24**	**94**
4	$Pd(OAc)_2$ (10)	3	Ag_2CO_3	24	87
5	$Pd(OAc)_2$ (10)	2.5	AgOAc	24	81
6	$Pd(OAc)_2$ (10)	2	AgOAc	24	67
7	$Pd(OAc)_2$ (10)	3	AgOAc	2	81
8	$Pd(OAc)_2$ (10)	0.5	AgOAc	2	0
9	$Pd(OAc)_2$ (10)	1	AgOAc	2	<5
10	$Pd(OAc)_2$ (10)	2	AgOAc	2	60
11	$Pd(OAc)_2$ (10)	2.5	AgOAc	2	67
12	$Pd(OAc)_2$ (5)	3	AgOAc	2	37
13[b]	$Pd(OAc)_2$ (10)	3	AgOAc (0.06 mmol)	24	0
14[b]	$Pd(OAc)_2$ (10)	3	AgOAc (0.15 mmol)	24	0
15[c]	$Pd(OAc)_2$ (10)	**4b**: 0.3	AgOAc (0.66 mmol)	24	**5b**: 32
16[c]	$Pd(OAc)_2$ (10)	**4b**: 0.6	AgOAc (0.66 mmol)	24	**5b**: 40
17[c]	$Pd(OAc)_2$ (10)	**4b**: 0.9	AgOAc (0.66 mmol)	24	**5b**: 46
18[c]	$Pd(OAc)_2$ (10)	**4b**: 1.2	AgOAc (0.66 mmol)	24	**5b**: 62 (70)[b]

[a] Isolated yields are reported. Reactions were carried out using **2a** (0.5 mmol), **3a** (0.5 mmol) and ArI (2-3 mmol)[b] **2a** (0.3 mmol), **3a** (0.3 mmol) and ArI (1.8 mmol) in neat condition. [c] The reaction was performed in toluene (2 mL) using **2a** (0.3 mmol), **3a** (0.3 mmol) at 110 ^{o}C.

Then, we desired to reduce the reaction time and accordingly, the Pd(II)-catalyzed multicomponent-type arylation involving anhydride **2a** (1 equiv), **3a** (1 equiv), **4a** (6 equiv) and AgOAc was heated at 110 ^{o}C for only 2 h instead of 24 h. This reaction also afforded the product **5a** in good yield (81%, entry 7, Table 1). Having noted that the reaction can be performed in 2 h itself, then we screened the reaction using lesser equiv of ArI **4a** (1-5 equiv). However, the yields of the product **5a** was found to gradually decrease from 67 to 0% when the equiv of **4a** was gradually reduced from 5 to 1 equiv (entries 8-11, Table 1). The multicomponent reaction of anhydride **2a** (1 equiv), **3a** (1 equiv) and **4a** (6 equiv) using 5 mol% of the $Pd(OAc)_2$ catalyst instead of 10 mol% of the $Pd(OAc)_2$ catalyst gave the product **5a** in only 37% yield (entry 12, Table 1). We also screened the reaction using lesser equiv of AgOAc, however, the product **5a** was not obtained when AgOAc was used in catalytic amounts (entries 13 and 14, Table 1). Next, we intended to assess the yield of the arylation reaction in a solvent and accordingly, we performed the arylation of **2a** with varying amounts of ArI **4b** in a solvent (e.g. toluene). The reaction of **2a** and **3a** with varying amounts **4b** (1-4 equiv) in toluene afforded the product **5b** in low to satisfactory yields (32-62%, entries 15-18, Table 1). Thus, the results shown in entries 3 and 7 are the best reaction conditions, which gave the product **5a** in good yield under solvent free condition.

Next, we wished to find out the possibility of using some other DGs[2] that are similar to 8-aminoquinoline for performing the multicomponent-type β-C-H arylation of carboxamides involving anhydrides as substrates *via in situ* installation of DG. In this regard, initially we performed the Pd(II)-catalyzed sp^2 arylation benzoic anhydride (**2b**) with **4a** using 4-amino-2,1,3-benzothiadiazole (**3b**) as the DG.[5c] This multicomponent reaction involving **3b** as the DG afforded the bis β-C-H arylation product **6aA** in only 34% yield (Scheme 3). Next, we performed the arylation of **2b** with **4a** using 2-aminophenol (**3c**) as the DG.[8c] This multicomponent reaction involving **3c** as the DG also afforded the bis β-C-H arylation product **6bA** in only 30% yield (Scheme 3). Then, we performed the sp^2 arylation of **2b** involving other DGs, such as N^1,N^1-dimethylethane-1,2-diamine (**3d**)[3b] or 2-(methylthio)aniline (**3e**)[3b] or benzene-1,2-diamine (**3f**)[7c] and these DGs were found ineffective. Furthermore, we also performed the sp^3 arylation of **2a** involving the bidentate DGs **3d-f** and a weakly coordinating monodentate ligand 2,3,4,5,6-pentafluoroaniline (**3g**, Yu's ligand[2n]). The DGs **3d-g** were found ineffective for the sp^3 arylation of **2a** (Scheme 3). It is to be noted that the reaction involving

propionic anhydride and simple hexylamine also did not afford the sp^3 arylation product **6dA**. These trials indicated that 8-aminoquinoline (**3a**) is a relatively more effective bidentate DG for performing the multicomponent-type *β*-C-H arylation of carboxamides involving anhydrides as substrates *via in situ* installation of the DG (Table 1).



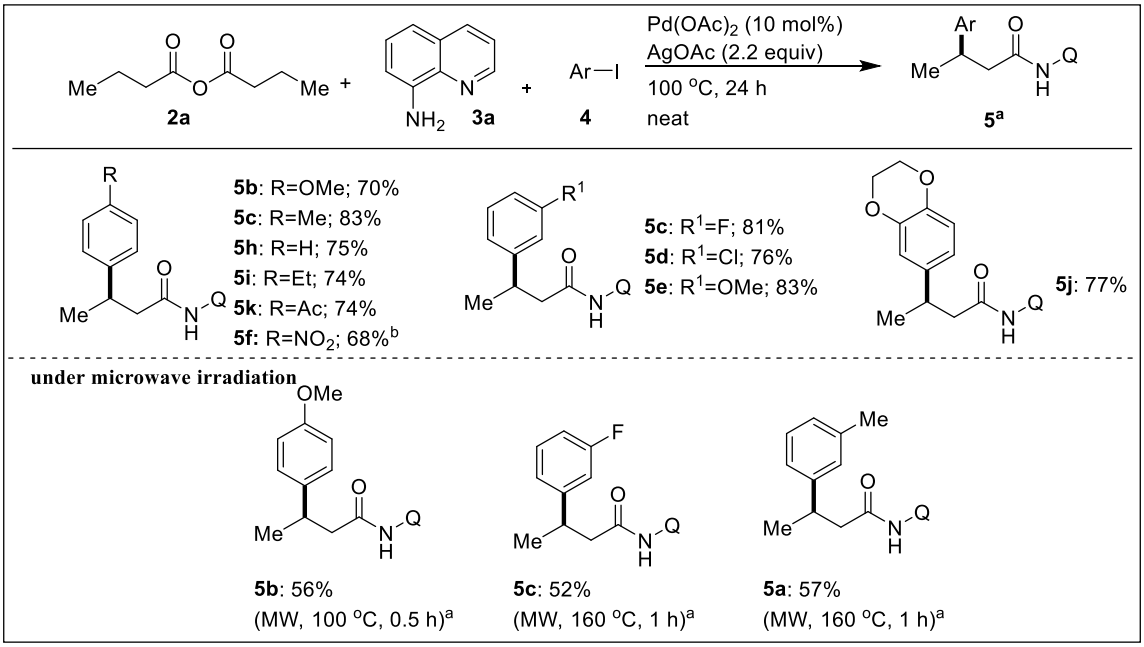
[a] Benzoic anhydride (**2b**, 0.5 mmol), **3b** (0.5 mmol), ArI (**4a**, 3 mmol), $Pd(OAc)_2$ (10 mol%), Ag_2CO_3 (1.1 mmol), neat, 100 °C, 24 h.[b] **2b** (0.5 mmol), **3c** (0.5 mmol), ArI (**4a**, 1.5 mmol), $Pd(OAc)_2$ (10 mol%), K_2CO_3 (1.1 mmol), MeCN (2 mL), 90 °C, 12 h.[c] Butyric anhydride (**2a**, 0.5 mmol), **3b-g** (0.5 mmol), ArI (**4a** or **4b**, 3 mmol), $Pd(OAc)_2$ (10 mol%), AgOAc (1.1 mmol), neat, 100 °C, 24 h. [d] Propionic anhydride (**2c**, 0.3 mmol), hexylamine (0.3 mmol), ArI (**4a** or **4b**, 1.5 mmol), $Pd(OAc)_2$ (10 mol%), AgTFA (0.9 mmol), neat, 120 °C, 48 h.

Scheme 3. C-H Arylation trials using other directing groups.

Having found the suitable reaction conditions and DG for the Pd(II)-catalyzed multicomponent-type reaction involving anhydride **2a**, **3a** and **4a**, which afforded the product **5a** in high yield (entry 3, Table 1). Next, we wished to extend the scope of this method dealing with one-pot arylation *via in situ* installation of DG. Accordingly, we carried out the Pd(II)-catalyzed multicomponent-type C-H arylation reaction involving butyric anhydride **2a**, **3a** and a variety of aryl iodides under solvent-free condition (Table 2). The Pd(II)-catalyzed, reaction involving butyric anhydride **2a**, **3a**, and PhI or other aryl iodides containing the electron-withdrawing and donating groups at the *meta* or *para* position afforded the *β*-C-H arylated products **5b-i,k** in good yields (68-83%, Table 2). The Pd(II)-catalyzed, multicomponent-type reaction involving butyric anhydride **2a**, **3a** and a di-substituted aryl iodide, e.g. 6-iodo-2,3-.

dihydrobenzo[*b*][1,4]dioxine also afforded the corresponding *β*-C-H arylated aliphatic carboxamide **5j** in 77% yield (Table 2).

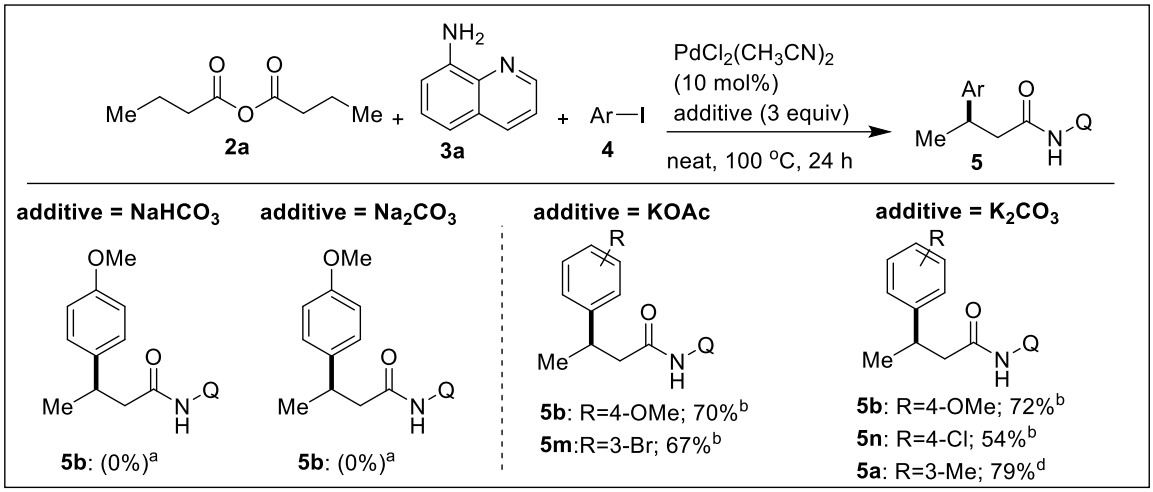
Table 2. Multicomponent one-pot Pd(II)-catalyzed C-H arylation of carboxamide **1c′** derived from anhydride **2a**[a]



[a] Isolated yields. Reactions were carried out using **2a** (0.5 mmol), **3a** (0.5 mmol) and ArI (2-3 mmol). Reactions affording **5b**, **5f** and **5k** were done using 0.3 mmol scale.
[b] Toluene (2 mL) was used.

In an attempt to improve the efficiency of this protocol, we attempted the multicomponent-type solvent free C-H arylation reaction of anhydride **2a**, **3a** with different aryl iodides under microwave irradiation and the corresponding C-H arylated carboxamides **5a-c** were obtained in 52-57% yields (Table 2). When compared to the reactions performed under conventional heating, the reactions under microwave irradiation afforded the C-H arylated carboxamides **5a-c** in only satisfactory yields. This is perhaps because the reaction of **2a**, **3a** and different aryl iodides were subjected to the microwave irradiation without any solvent and it is to be noted that in general the microwave reactions are efficient when performed using a solvent with high tan *δ*.

Conventionally, the Pd(II)-catalyzed C-H arylation reactions have been performed using a silver salt (e.g., AgOAc and Ag_2CO_3) as an additive, which functions as a scavenger for the iodide anion that is generated in the reaction and also implicitly helps in the regeneration of the Pd(II) catalyst in the catalytic cycle.[2-7] It is to be noted that some of the research papers have revealed the use of relatively inexpensive salts, such as K_2CO_3 and KOAc etc as the additives instead of silver salts.[2-7]



[a] Isolated yields are reported. **2a** (0.3 mmol), **3a** (0.3 mmol), ArI (1.8 mmol), $Pd(OAc)_2$ (10 mol%), $NaHCO_3/Na_2CO_3$ (0.7 mmol), neat, 100 °C, 36 h.[b] **2a** (0.3 mmol), **3a** (0.3 mmol) and ArI (2-3 mmol). [c] Reaction was performed using hexanoic anhydride. [d] **2a** (0.5 mmol), **3a** (0.5 mmol) and ArI (2-3 mmol).

Table 3. The Pd(II)-catalyzed C-H arylation of anhydride **2a** using additives other than silver salts.

Recently, Chen and Quin[6] introduced CsOAc as an additive for the conventional two-step process comprising Pd(II)-catalyzed arylation of carboxamides. Along this line, we also performed the Pd(II)-catalyzed multicomponent reaction of anhydride **2a** (1 equiv), **3a** (1 equiv) and ArI using KOAc or K_2CO_3 as an additive (Table 3). Accordingly, the C-H arylated aliphatic carboxamides **5b,l,m** were obtained in 43-70% yields using KOAc as an additive. Similarly, the C-H arylated aliphatic carboxamides **5a,b,n** were also obtained in 54-79% yields using K_2CO_3 as an additive. The yields obtained for the C-H arylated aliphatic carboxamides **5a,b,l,m,n** using KOAc or K_2CO_3 or AgOAc as an additive were comparable (Tables 1-3).

Then, to extend the substrate scope we intended to carry out the multicomponent-type Pd(II)-catalyzed *β*-C-H arylation of carboxamides using different aliphatic anhydrides as substrates. Accordingly, we treated hexanoic anhydride (**2d**), 8-aminoquinoline, (**3a**) with PhI or different aryl iodides in the presence of the $Pd(OAc)_2$ catalyst (10 mol%) and AgOAc as an additive at 110 °C for 24 h under solvent-free condition. These reactions afforded the corresponding *β*-C-H arylated hexanamides **6a-d** in 62-76% yields (Table 4). Next, we performed the Pd(II)-catalyzed reaction of valeric (pentanoic) anhydride (**2e**), **3a** with different mono or di-substituted aryl iodides, which afforded the corresponding *β*-C-H arylated pentanamides **7a-g** in 52-90% yields.

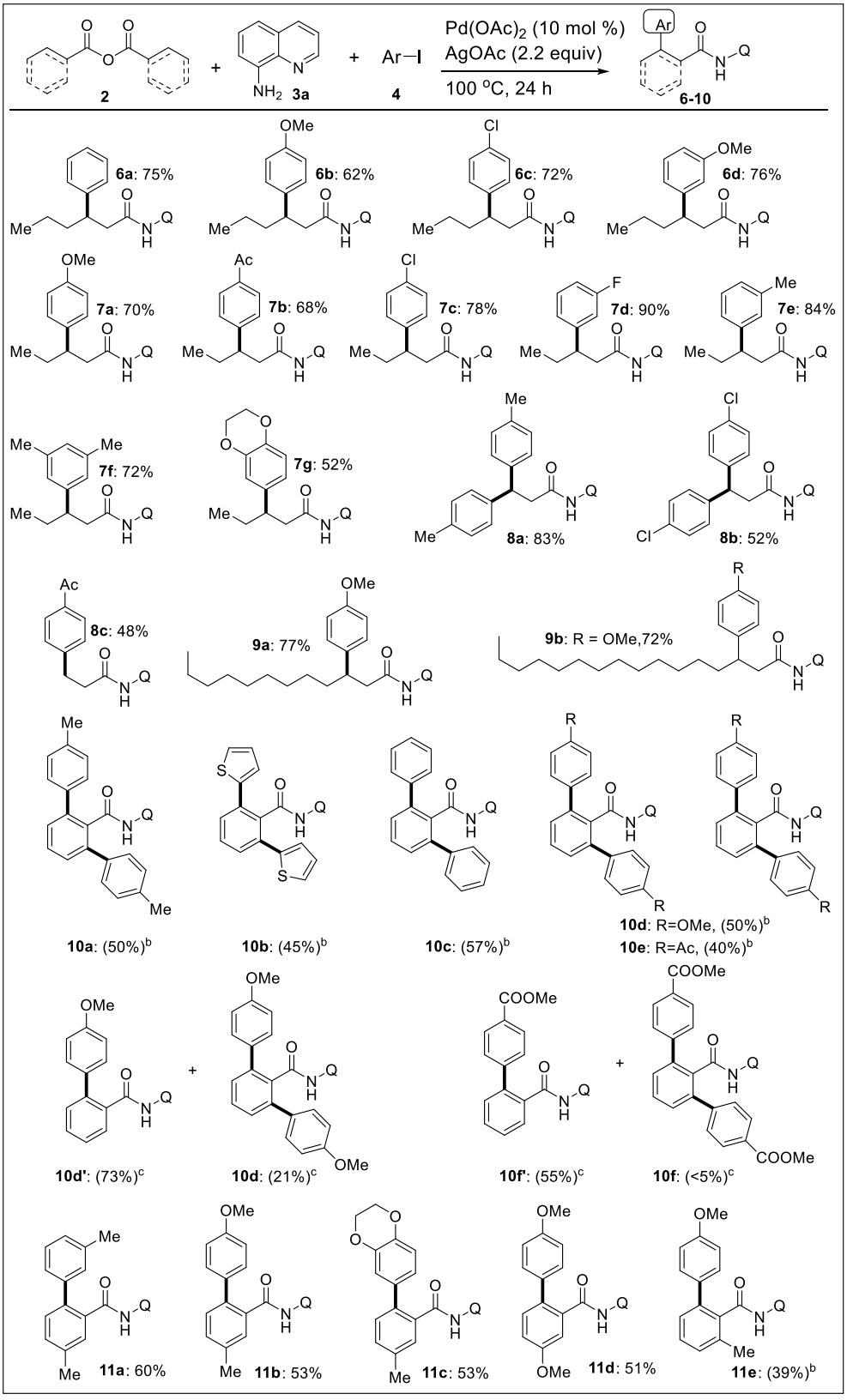
The Pd(II)-catalyzed reaction of propionic anhydride (**2c**), **3a** with aryl iodides containing electron donating or mild withdrawing groups at the *para* position afforded the corresponding bis *β*-C-H arylated propionamides (diarylmethanes) **8a,b** in 52-83% yields (Table 4). The observed bis *β*-C-H arylation of propionamide derived *in situ* from propionic anhydride (**2f**)

and **3a** with aryl iodides containing electron donating or mild withdrawing groups at the *para* position is in accordance with the literature reports.[3b,5c] On other hand, the Pd(II)-catalyzed reaction of propionic anhydride (**2c**), **3a** with an aryl iodide containing electron withdrawing groups at the *para* position afforded the mono *β*-C-H arylated propionamide **8c** in 48% yield. This observation is also in accordance with the literature reports.[3b,5c] In general, the Pd(II)-catalyzed arylation of methylene *β*-C-H bonds of aliphatic carboxamides (generated from carboxylic acid derivatives other than propionic acid) have led to the mono arylation products containing tertiary C-H bonds and further arylation of the tertiary sp^3 C-H bonds are relatively challenging. Often, the arylation of primary (methyl) *β*-C-H bonds of propionamides have afforded the bis *β*-C-H arylation products. This is perhaps the mono arylation of propionamide results into a relatively reactive (benzylic) methylene *β*-C-H bond which further undergo a second arylation to afford the bis *β*-C-H arylation products (e.g. **8a,b**).[3b,5c]

Then, we carried out the multicomponent-type Pd(II)-catalyzed sp^3 *β*-C-H arylation of carboxamides involving fatty acid anhydrides as substrates. Accordingly, the Pd(II)-catalyzed reaction of dodecanoic anhydride (**2f**) or palmitic anhydride (**2g**) and **3a** with different aryl iodides afforded the corresponding *β*-C-H arylated aliphatic carboxamides **9a,b** in 72-77% yields (Table 4). Subsequently, we intended to carry out the multicomponent-type Pd(II)-catalyzed *β*-C-H arylation of benzamides involving aromatic anhydrides as substrates *via in situ* installation of DG. In this regard, we treated benzoic anhydride (**2b**), **3a** with *p*-tolyl iodide (6 equiv) in the presence of the $Pd(OAc)_2$ catalyst (10 mol%) and AgOAc as an additive under solvent-free condition. We observed that the reaction was sluggish and not fruitful under solvent-free condition and this is perhaps due to the non-homogeneousness of the reaction mixture and poor mixing of benzoic anhydride (or *in situ* generated benzamide) under solvent-free condition.

Then, we treated benzoic anhydride (**2b**), **3a** with *p*-tolyl iodide (6 equiv) in the presence of the $Pd(OAc)_2$ catalyst (10 mol%) and AgOAc as an additive in toluene, which afforded the bis *β*-C-H arylation product **10a** in 50% yield (Table 4). Then, we carried out the Pd(II)-catalyzed, multicomponent-type C-H arylation reaction involving benzoic anhydride **2b**, **3a** with a variety of aryl iodides to afford the corresponding bis *β*-C-H arylation products **10b-e** in 40-57% yields (Table 4).

Table 4. Multicomponent Pd(II)-catalyzed C-H arylation of various carboxamides derived from their anhydrides[a]



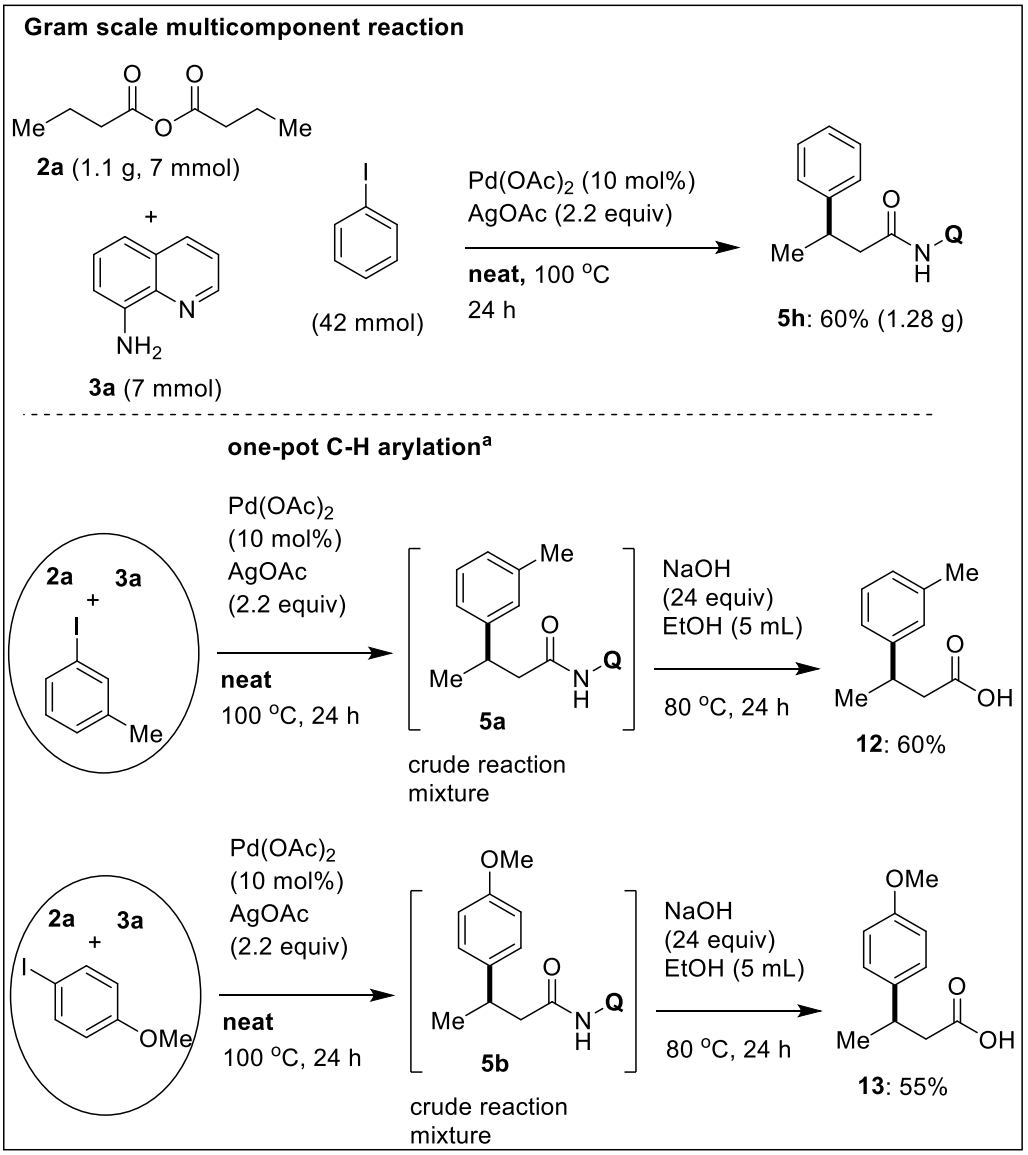
[a] Isolated yields are reported. Reactions were done using **3a** (0.5 mmol) and ArI (2-3 mmol) and 0.5 mmol of the corresponding anhydride **2** ((hexanoic anhydride (**2d**), valeric anhydride (**2e**), propionic anhydride (**2c**), dodecanoic anhydride (**2f**), palmitic anhydride (**2g**), 3-methylbenzoic anhydride (**2h**), 3-methoxybenzoic anhydride (**2i**) and 2-methybenzoic anhydride (**2j**)). Reactions afforded **6d**, **7b-e**, **9a,b**, **10b**, **10d′** and **10f′** were done using 0.3 mmol of

2.[b] Reactions were done using anhydride **2b/2j** (0.5 mmol), **3a** (0.5 mmol), ArI (2-3 mmol), $Pd(OAc)_2$ (10 mol%) and AgOAc (1.1 mmol) in toluene (2 mL), 110 °C, 24-36 h. [c] Reactions were done using **2b** (0.3 mmol), **3a** (0.3 mmol), ArI (1-1.5 mmol), $Ni(OTf)_2$ (10 mol%), Na_2CO_3 (1 mmol), toluene, 160 °C, 36 h.

In accordance with the literature,[3b,5c,4b] the Pd(II)-catalyzed C-H arylation reactions involving benzoic anhydride (**2b**), 8-aminoquinoline (**3a**) with aryl iodides also afforded the corresponding bis *β*-C-H arylation products **10** as the major compounds and the corresponding mono *β*-C-H arylation products **10′** were not obtained in characterizable amounts (Table 4).

Then, we also desired to obtain the mono *β*-C-H arylation products **10′** using anhydrides as substrates. Accordingly, we have performed the multicomponent-type C-H arylation reaction involving anhydride **2b**, **3a** and ArI using the $Ni(OTf)_2$ catalyst (reported by Chatani)[8d] instead of the $Pd(OAc)_2$ catalyst. These reactions gave the corresponding mono *β*-C-H arylation products **10d′** (73%) and **10f′** (55%) as the major compounds along with the corresponding bis *β*-C-H arylation products **10d** (21%) and **10f** (<5%) as the minor compounds (Table 4). These results indicated that the Ni-catalyzed reactions are relatively slower when compared to the Pd-catalyzed reaction and accordingly, the mono *β*-C-H arylation product can be obtained *via* the Ni-catalyzed reactions (Table 4).

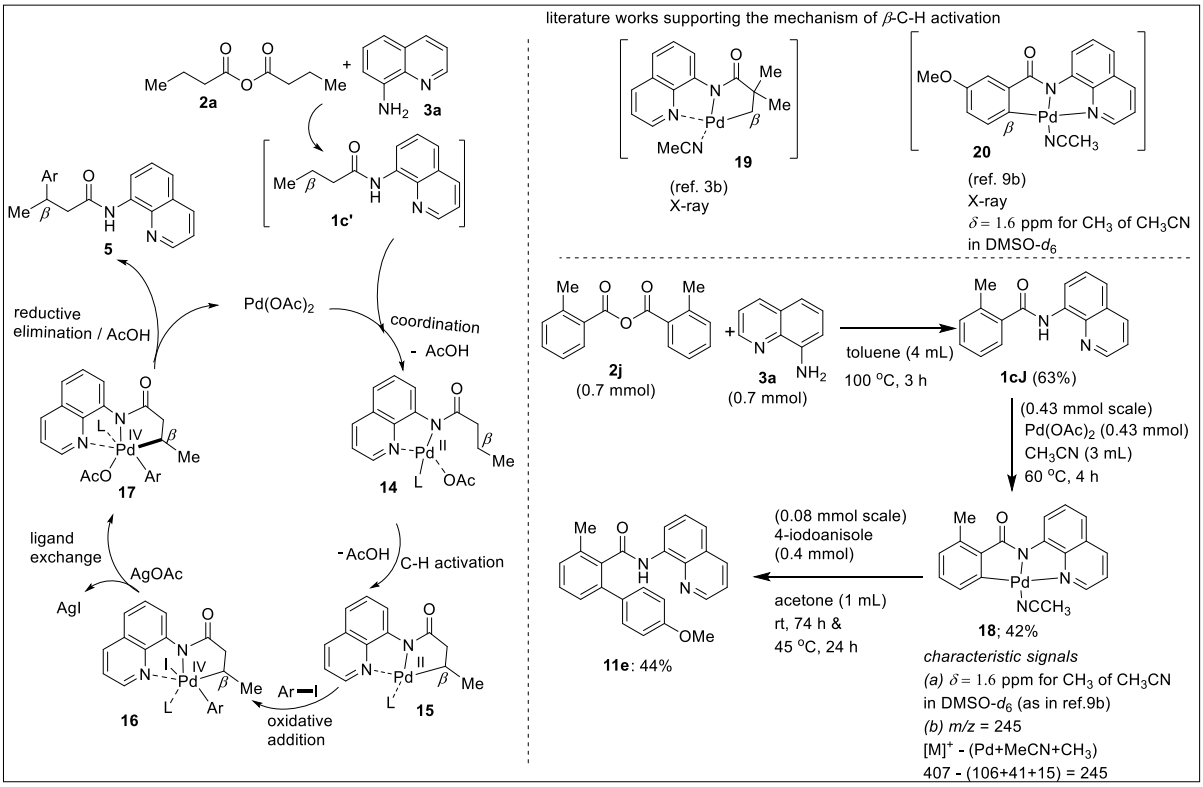
Next, to extend the sp^2 C-H arylation reaction involving different aromatic anhydrides, we assembled 3-methylbenzoic anhydride (**2h**), 3-methoxybenzoic anhydride (**2i**) and 2-methybenzoic anhydride (**2j**) and then subjected them to the Pd(II)-catalyzed multicomponent C-H arylation reaction under solvent-free condition. The Pd(II)-catalyzed reaction comprising 3-methylbenzoic anhydride **2h**, **3a** and different aryl iodides afforded the corresponding mono *β*-C-H arylation products **11a-c** in 53-60% yields (Table 4). Similarly, the Pd(II)-catalyzed, multicomponent C-H arylation reaction involving **2i** or **2j**, **3a** and *p*-anisyl iodide afforded the corresponding mono *β*-C-H arylation products **11d** and **11e** in 39-51% yields (Table 4). In accordance with literature, the C-H arylation reactions of benzamides involving benzoic anhydrides **2h,i** and **3a** with aryl iodides afforded the corresponding mono *β*-C-H arylation products **11**[3b,5c,4b] and the corresponding bis *β*-C-H arylation products were not obtained in characterizable amounts. This is perhaps the substituent present in the *meta* position of the corresponding benzamides derived from anhydrides **2h,i** presumably imparts the steric hindrance for the second *β*-C-H arylation reaction.



Scheme 4. Gram scale multicomponent reaction and directing group removal.

We also attempted the Pd(II)-catalyzed, multicomponent-type C-H arylation reaction in a gram scale and accordingly, we heated a mixture of butyric anhydride (**2a**), **3a**, PhI, $Pd(OAc)_2$ and AgOAc at 110 °C for 24 h under solvent-free condition. This reaction afforded the *β*-C-H arylated aliphatic carboxamide **5h** in 60% yield (1.28 g, Scheme 4). Further, it is to be noted that generally the removal of the DGs was carried out using C-H arylated carboxamides, which were obtained after the column chromatographic purification process. It was envisaged to perform the DG removal after the multicomponent C-H arylation reaction by avoiding the column chromatographic purification process.[4] In this regard, after the multicomponent C-H arylation reaction, the crude reaction mixture containing the C-H arylated carboxamide **5a** or **5b** was subjected to the amide hydrolysis reaction condition to afford the corresponding carboxylic acids **12** and **13** in satisfactory yields (55-60%, Scheme 4).

Scheme 5 shows a plausible mechanism for the multicomponent reaction in accordance with the generally accepted proposed mechanism[2,9] for the Pd(II)-catalyzed, AgOAc-promoted, DG-assisted C-H activation of carboxamides. The mechanism involves the following steps after the *in situ* formation of carboxamide **1c′** from **2a** and **3a**: (a) An initial coordination of the DG of carboxamide **1c′** to the $Pd(OAc)_2$ catalyst and followed by the C(β)−H activation generates the palladium(II) species **15**. (b) The palladium species **15** undergoes oxidative addition with an ArI to generate the palladium(IV) species **16**. (c) Then, AgOAc acts as an iodide ion scavenger in the ligand exchange step to generate the palladium(IV) species **17**. (d) Next, the reductive elimination of the palladium(IV) species **17** yields the C(β)−H arylated product **5** along with the regeneration of the Pd(II) catalyst.[10]



Scheme 5. Proposed mechanism of multicomponent one-pot Pd(II)-catalyzed β-C-H arylation of carboxamide derived from anhydride.[10]

In summary, we have shown a one-pot, solvent free, multicomponent-type reaction comprising the Pd(II)-catalyzed DG-assisted β-C-H arylation of carboxamides involving anhydrides as substrates *via in situ* installation of DG. It is to be noted that typically, the DG-assisted β-C-H arylation of carboxamides is a two-step process comprising the installation of DG in a carboxylic acid or its derivative (e.g., acid chloride) and then, the Pd(II)-catalyzed C-H arylation. In this paper, we have shown the multicomponent-type Pd(II)-catalyzed β-C-H arylation of carboxamides involving anhydrides as substrates *via in situ* installation of DG.

Different anhydrides, DGs, aryl iodides and catalysts and additives were screened to establish the scope of the C-H arylation reaction process and various *β*-C-H arylated carboxamides were obtained in satisfactory to good yields. This work will be a contribution with regard to the development of simple and multicomponent-based C-H activation reactions.

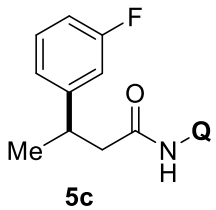
Experimental Section

General information. ^{1}H and ^{13}C NMR spectra of all compounds were recorded in 400 and ~101 MHz spectrometers (using TMS as an internal standard), respectively. The HRMS data of samples were obtained from QTOF mass analyzer using ESI method. IR spectra of samples were recorded as neat or thin films. Column chromatography purification was carried out on silica gel (100−200 mesh). TLC analyses were performed on silica gel or alumina plates and components were visualized by observation under iodine vapor. Reactions were performed in dry solvents under a nitrogen atm wherever required. Isolated yields of all the C-H arylated products are reported and yields were not optimized.

The compounds **5a**,[4a] **5b**,[6] **5d**,[4a] **5e**,[6] **5f**,[4a] **5g**,[4a] **5h**,[4a] **5k**,[7a] **5l**,[6] **5m**,[6] **5n**,[6] **6a**,[4c] **6b**,[4c] **6c**,[4c] **7a**,[7b] **8a**,[5a] **9a**,[4a] **10a**,[4b] **10c**,[4b] **10d′**,[7c] **10d**,[4b] **10e**,[4b] **11b**,[7d] **11d**,[7e] **12**,[8a] **13**,[8b] **11e**,[7e] and **1cJ**[7f] are reported in the literature.

3.2. General experimental procedure for the multicomponent, solvent-free Pd(II)-catalyzed direct *β*-C-H arylation of carboxamides involving anhydrides as substrates *via in situ* installation of the DG: A mixture of anhydride (**2**,1 equiv), DG (8-aminoquinoline, **3a**, 1 equiv), ArI (4-6 equiv), $Pd(OAc)_2$ (10 mol%) and AgOAc (1.1 mmol) was heated at 110 ^{o}C for an appropriate time (2-24 h, see the corresponding Tables/Schemes for exact time and other specific conditions). Then, reaction mixture was cooled to rt, filtered on celite® (EtOAc was used as a washing solvent) and the filtrate was treated with aq. $NaHCO_3$ solution and then, extracted using EtOAc. The combined organic layers were dried over anhydrous Na_2SO_4 and evaporated to afford the crude reaction mixture. Then, the crude reaction mixture was subjected to the column chromatographic purification (EtOAc:Hexane = 20:80) to give the corresponding C-H arylated product (see the respective Tables/Schemes for the specific entries).

3.2.1. 3-(3-Fluorophenyl)-*N*-(quinolin-8-yl)butanamide (5c): Following the general procedure, **5c** was obtained after purification by column chromatography on silica gel (EtOAc:

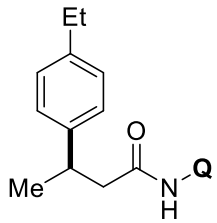


5c

Hexane = 20:80) as a brown colour oil (126 mg, 81%); R_f = 0.5 (EtOAc:Hexane = 20:80); FTIR (DCM): 3351, 2967, 1691, 1589 and 1528 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.75 (s, 1H), 8.80 – 8.77 (m, 2H), 8.16 (d, 1H, *J* = 8.2 Hz), 7.54 – 7.44 (m, 3H), 7.28 - 7.24 (m, 1H),

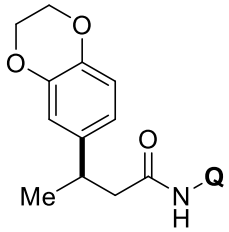
7.14 – 7.05 (m, 2H), 6.90 (t, 1H, J = 8.3 Hz), 3.54 – 3.51 (m, 1H), 2.92 - 2.87 (m, 1H), 2.82 – 2.76 (m, 1H), 1.43 (d, 3H J = 6.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.9, 163.1 (d, $J_{C\text{-}F}$ = 243 Hz), 148.6 (d, $J_{C\text{-}F}$ = 6.9 Hz), 148.1, 138.3, 136.3, 134.3, 130 (d, $J_{C\text{-}F}$ = 8.1 Hz), 127.9, 127.4, 122.7 (d, $J_{C\text{-}F}$ = 2.5 Hz), 121.6, 121.5, 116.5, 113.7 (d, $J_{C\text{-}F}$ = 21.1 Hz), 113.3 (d, $J_{C\text{-}F}$ = 20.8 Hz), 46.6, 36.6, 21.7; ^{19}F NMR (~376 MHz, $CDCl_3$): δ = –113.2; HRMS (ESI): MH^+, found 309.1393. $C_{19}H_{18}FN_2O$ requires 309.1403.

3.2.2. 3-(4-Ethylphenyl)-*N*-(quinolin-8-yl)butanamide (5i): Following the general procedure, **5i** was obtained after purification by column chromatography on silica gel (EtOAc:Hexane = 20:80) as a colourless solid (117 mg, 74%); R_f = 0.5 (EtOAc:Hexane = 20:80); mp 69 – 70 ^{o}C; FTIR (DCM): 3354, 2963, 1686, 1526 and 1484 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.78 (s, 1H), 8.83 – 8.79 (m, 2H), 8.15 (d, 1H, J = 8.2 Hz), 7.56 – 7.49 (m, 2H), 7.45 (dd, 1H, J_1 = 8.2 Hz, J_2 = 4.2 Hz), 7.29 (d, 2H, J = 7.6 Hz), 7.19 (d, 2H, J = 7.6 Hz), 3.55 – 3.49 (m, 1H), 2.92 (dd, 1H, J_1 = 14.4 Hz, J_2 = 6.4 Hz), 2.79 (dd, 1H, J_1 = 14.4 Hz, J_2 = 8.4 Hz), 2.63 (q, 2H, J = 7.6 Hz), 1.44 (d, 3H, J = 6.9 Hz), 1.23 (t, 3H, J = 7.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.5, 148.1, 143.2, 142.2, 138.3, 136.3, 134.5, 128.1, 127.9, 127.4, 126.8, 121.6, 121.4, 116.4, 47.0, 36.5, 28.4, 21.9, 15.6; HRMS (ESI): MH^+, found319.1794. $C_{21}H_{23}N_2O$ requires 319.1810.



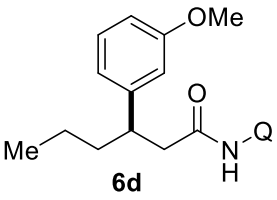
5i

3.2.3. 3-(2,3-Dihydrobenzo[*b*][1,4]dioxin-6-yl)-*N*-(quinolin-8-yl)butanamide (5j): Following the general procedure, **5j** was obtained after purification by column chromatography on silica gel (EtOAc:Hexane = 20:80) as a brown colour solid (133 mg, 77%); R_f = 0.4 (EtOAc:Hexane = 20:80); mp 96 – 98 ^{o}C; FTIR (DCM): 3352, 2965, 1682, 1589 and 1526 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.74 (s, 1H), 8.79 – 8.76 (m, 2H), 8.13 – 8.08 (m, 1H), 7.51 – 7.4 (m, 3H), 6.87 – 6.82 (m, 3H), 4.20 – 4.19 (m, 4H), 3.45 – 3.40 (m, 1H), 2.86 (dd, 1H, J_1 = 14.4 Hz, J_2 = 6.8 Hz), 2.73 (dd, 1H, J_1 = 14.8, J_2 = 8.0 Hz), 1.39 (d, 3H, J = 6.9 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.4, 148.1, 143.5, 142.0, 139.4, 138.3, 136.3, 134.4, 127.9, 127.4, 121.6, 121.4, 119.8, 117.3, 116.4, 115.5, 64.4, 64.3, 47.0, 36.3, 22.0; HRMS (ESI): MH^+, found 349.1535. $C_{21}H_{21}N_2O_3$ requires 349.1552.



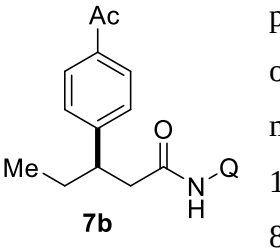
5j

3.2.4. 3-(3-Methoxyphenyl)-*N*-(quinolin-8-yl)hexanamide (6d): Following the general procedure, **6d** was obtained after purification by column chromatography on silica gel (EtOAc:Hexane = 20:80) as a colourless thick liquid (80 mg, 76%); R_f = 0.5 (EtOAc:Hexane = 20:80); FTIR (DCM): 3353, 2929, 1684, 1595 and 1528 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 9.71 (s, 1H), 8.78 – 8.76 (m, 2H), 8.13 (d, 1H, J = 8.2 Hz), 7.54 – 7.42 (m, 3H), 7.25 – 7.21 (m, 1H), 6.92 – 6.87 (m, 2H), 6.73 (dd, 1H, J_1 = 8.2 Hz, J_2 = 2.4 Hz), 3.79 (s, 3H), 3.34 – 3.30 (m, 1H), 2.86 (d, 2H, J = 7.4 Hz), 1.80 – 1.68 (m, 2H), 1.32 – 1.23 (m, 2H), 0.89 (t, 3H, J = 7.3 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.4, 159.7, 148.0, 146.1, 138.3, 136.3, 134.4, 129.5, 127.9, 127.4, 121.5, 121.4, 120.0, 116.4, 113.4, 111.6, 55.1, 45.9, 42.5, 38.4, 20.6, 14.1; HRMS (ESI): MH^+, found 349.1925 $C_{22}H_{25}N_2O_2$ requires 349.1916.



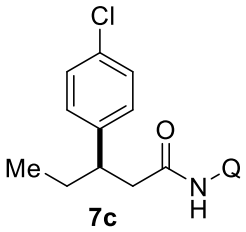
6d

3.2.5. 3-(4-Acetylphenyl)-*N*-(quinolin-8-yl)pentanamide (7b): Following the general procedure, **7b** was obtained after purification by column chromatography on silica gel (EtOAc:Hexane = 20:80) as a brown colour semi solid (70 mg, 68%); R_f = 0.4 (EtOAc:Hexane = 20:80); FTIR (DCM): 3350, 2963, 1681, 1606 and 1575 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 9.69 (s, 1H), 8.74 (dd, 1H, J_1 = 4.2 Hz, J_2 = 1.4 Hz), 8.70 (dd, 1H, J_1 = 6.7 Hz, J_2 = 2.0 Hz), 8.12 (dd, 1H, J_1 = 8.2 Hz, J_2 = 1.4 Hz), 7.89 (d, 1H, J = 8.2 Hz), 7.51 – 7.40 (m, 3H), 7.39 (d, 1H, J = 8.2 Hz), 3.33 – 3.30 (m, 1H), 2.95 -2.82 (m, 2H), 2.54 (s, 3H), 1.91 – 1.86 (m, 1H), 1.78 – 1.70 (m, 1H), 0.85 (t, 3H, J = 7.3 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 197.8, 169.9, 149.9, 148.1, 138.2, 136.3, 135.6, 134.3, 128.7, 127.9, 127.9, 127.3, 121.6, 121.5, 116.4, 45.0, 44.3, 29.0, 26.6, 12.0; HRMS (ESI): MH^+, found 347.1752 $C_{22}H_{23}N_2O_2$ requires 347.1760.



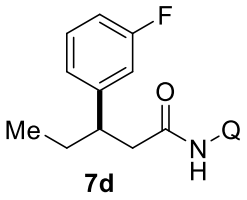
7b

3.2.6. 3-(4-Chlorophenyl)-*N*-(quinolin-8-yl)pentanamide (7c): Following the general procedure, **7c** was obtained after purification by column chromatography on silica gel (EtOAc:Hexane = 20:80) as colourless thick liquid (80 mg, 78%); R_f = 0.5 (EtOAc:Hexane = 20:80); FTIR (DCM): 3351, 2928, 1682, 1529 and 1485 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 9.67 (s, 1H), 8.78 (dd, 1H, J_1 = 4.2 Hz, J_2 = 1.4 Hz), 8.73 (dd, 1H, J_1 = 6.8 Hz, J_2 = 2.0 Hz), 8.16 (dd, 1H, J_1 = 8.3 Hz, J_2 = 1.4 Hz), 7.54 – 7.44 (m, 3H), 7.27 (d, 2H, J = 7.3 Hz), 7.24 (d, 2H, J = 7.3 Hz), 3.24 – 3.20 (m, 1H), 2.92 – 2.78 (m, 2H), 1.90 – 1.84 (m, 1H), 1.73 – 1.69 (m, 1H), 0.85 (t, 3H, J = 7.3 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.1, 148.1, 142.5, 138.2, 136.3, 134.3, 132.0, 129.0, 128.7, 127.9, 127.4, 121.6, 121.5, 116.4, 45.4, 43.8, 29.1, 12.0; HRMS (ESI): MH^+, found 339.1279 $C_{20}H_{20}ClN_2O$ requires 339.1264.



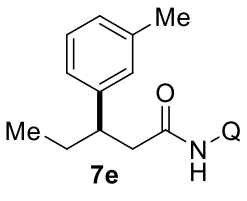
7c

3.2.7. 3-(3-Fluorophenyl)-*N*-(quinolin-8-yl)pentanamide (7d): Following the general procedure, **7d** was obtained after purification by column chromatography on silica gel (EtOAc:Hexane = 20:80) as a colourless semi liquid (87 mg, 90%); R_f = 0.5 (EtOAc:Hexane = 20:80); FTIR (DCM): 3352, 2929, 1684, 1589 and 1527 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 9.71 (s, 1H), 8.79 (dd, 1H, J_1 = 4.0 Hz, J_2 = 1.0 Hz), 8.74 (dd, 1H, J_1 = 6.9 Hz, J_2 = 1.7 Hz), 8.16 (dd, 1H, J_1 = 8.2 Hz, J_2 = 1.0 Hz), 7.55 – 7.44 (m, 3H), 7.28 – 7.23 (m, 1H), 7.09 (d, 1H, J = 7.7 Hz), 7.03 (d, 1H, J = 10.1 Hz), 6.88 (td, 1H, J_1 = 8.5 Hz, J_2 = 2.4 Hz), 3.27 – 3.24 (m, 1H), 2.92 – 2.81 (m, 2H), 1.91 – 1.85 (m, 1H), 1.75 – 1.69 (m, 1H), 0.87 (t, 3H, J = 7.3 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.1, 163.1 (d, $J_{C\text{-}F}$ = 243 Hz), 148.1, 146.8 (d, $J_{C\text{-}F}$ = 6.8 Hz), 138.2, 136.3, 134.3, 129.9 (d, $J_{C\text{-}F}$ = 8.1 Hz), 127.9, 127.4, 123.5 (d, $J_{C\text{-}F}$ = 2.7 Hz), 121.6, 121.4, 116.4, 114.3 (d, $J_{C\text{-}F}$ = 20.9 Hz), 113.3 (d, $J_{C\text{-}F}$ = 21 Hz), 45.3, 44.1 (d, $J_{C\text{-}F}$ = 1.3 Hz), 29.1, 12.0; HRMS (ESI): MH^+, found 323.1576. $C_{20}H_{20}FN_2O$ requires 323.1560.



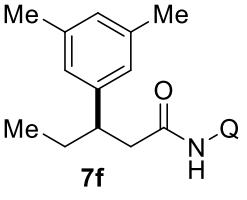
7d

3.2.8. *N*-(Quinolin-8-yl)-3-(*m*-tolyl)pentanamide (7e): Following the general procedure, **7e** was obtained after purification by column chromatography on silica gel (EtOAc:Hexane = 20:80) as a colourless semi liquid (81 mg, 84%); R_f = 0.6 (EtOAc:Hexane = 20:80); FTIR (DCM): 3366, 2926, 1684, 1527 and 1484 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 9.73 (s, 1H), 8.78 – 8.77 (m, 2H), 8.14 (d, 1H, J = 8.2 Hz), 7.54 – 7.42 (m, 3H), 7.23 – 7.19 (m, 1H), 7.14 – 7.11 (m, 2H), 7.01 (d, 1H, J = 7.4 Hz), 3.23 – 3.17 (m, 1H), 2.88 (d, 2H, J = 7.4 Hz), 2.34 (s, 3H), 1.92 – 1.85 (m, 1H), 1.77 – 1.69 (m, 1H), 0.87 (t, 3H, J = 7.3 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.6, 148.0, 144.0, 138.3, 138.0, 136.3, 134.5, 128.4, 128.4, 127.9, 127.4, 127.2, 124.7, 121.5, 121.4, 116.4, 45.6, 44.3, 29.2, 21.5, 12.1; HRMS (ESI): MH^+, found 319.1823. $C_{21}H_{23}N_2O$ requires 319.1810.



7e

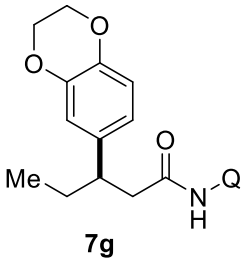
3.2.9. 3-(3,5-Dimethylphenyl)-*N*-(quinolin-8-yl)pentanamide (7f): Following the general procedure, **7f** was obtained after purification by column chromatography on silica gel (EtOAc:Hexane = 20:80) as a colourless solid (119 mg, 70%); R_f = 0.5 (EtOAc:Hexane = 20:80); mp 74 – 75 ^oC; FTIR (DCM): 3355, 2924, 1689, 1602 and 1529 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 9.71 (s, 1H), 8.79 – 8.76 (m, 2H), 8.16 (dd, 1H, J_1 = 8.3 Hz, J_2 = 1.6 Hz), 7.55 – 7.44 (m, 3H), 6.92 (s, 2H), 6.82 (s, 1H), 3.17 – 3.12 (m, 1H), 2.86 (d, 2H, J = 7.4 Hz), 2.29 (s, 6H), 1.89 – 1.82 (m, 1H), 1.75 – 1.69 (m, 1H), 0.86 (t, 3H, J = 7.3 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ



7f

170.7, 148.0, 144.0, 138.3, 137.8, 136.3, 134.5, 128.1, 127.9, 127.4, 125.4, 121.5, 121.3, 116.4, 45.6, 44.2, 29.1, 21.4, 12.1; HRMS (ESI): MH^+, found 333.1957 $C_{22}H_{25}N_2O$ requires 333.1967.

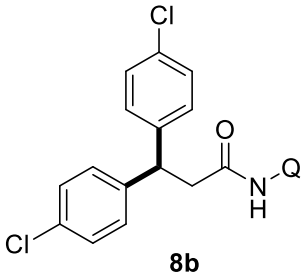
3.2.10. 3-(2,3-Dihydrobenzo[*b*][1,4]dioxin-6-yl)-*N*-(quinolin-8-yl)pentanamide (7g):



7g

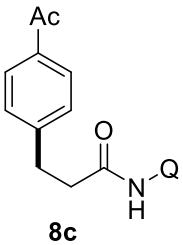
Following the general procedure, **7g** was obtained after purification by column chromatography on silica gel (EtOAc:Hexane = 20:80) as a colourless semi solid (93 mg, 52%); R_f = 0.5 (EtOAc:Hexane = 20:80); FTIR (DCM): 3352, 2928, 1682, 1589 and 1526 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 9.70 (s, 1H), 8.79 – 8.75 (m, 2H), 8.15 (d, 1H, *J* = 8.2 Hz), 7.54 – 7.43 (m, 3H), 6.81 – 6.80 (m, 3 H), 4.21 (s, 4H), 3.14 – 3.10 (m, 1H), 2.83 – 2.81 (m, 2H), 1.85 – 1.80 (m, 1H), 1.70 – 1.62 (m, 1H), 0.86 (t, 3H, *J* = 7.32 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.5, 148.0, 143.4, 142.0, 138.3, 137.4, 136.3, 134.5, 127.9, 127.4, 121.5, 121.3, 120.6, 117.2, 116.4, 116.1, 64.4, 64.3, 45.7, 43.7, 29.2, 12.0; HRMS (ESI): MH^+, found 363.1726. $C_{22}H_{23}N_2O_3$ requires 363.1709.

3.2.11. 3,3-Bis(4-chlorophenyl)-*N*-(quinolin-8-yl)propanamide (8b): Following the general procedure, **8b** was obtained after purification by column chromatography on silica gel (EtOAc:Hexane = 20:80) as a colourless solid (65 mg, 60%); R_f = 0.6 (EtOAc:Hexane = 20:80); mp 163 – 165 ^oC; FTIR (DCM): 3337, 2920, 1669, 1524 and 1485 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 9.77 (s, 1H), 8.78 (d, 1H, *J* = 4.1 Hz), 8.71 (dd, 1H, J_1 = 5.2 Hz, J_2 = 3.6 Hz), 8.15 (d, 1H, *J* = 7.7 Hz), 7.53 – 7.44 (m, 3H), 7.29 – 7.24 (m, 8H), 4.76 (t, 1H, *J* = 7.7 Hz), 3.27 (d, 2H, *J* = 7.7 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 168.9, 148.1, 141.8, 138.2, 136.4, 134.1, 132.5, 129.1, 128.9, 127.9, 127.3, 121.7, 121.7, 116.6, 45.9, 44.1; HRMS (ESI): MH^+, found 421.0896 $C_{24}H_{19}Cl_2N_2O$ requires 421.0874.



8b

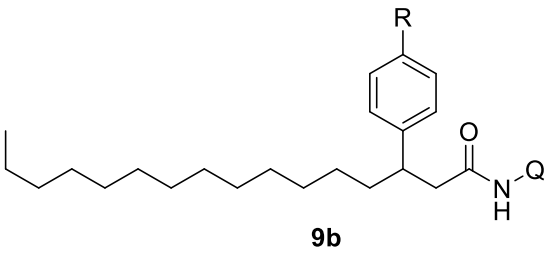
3.2.12. 3-(4-Acetylphenyl)-*N*-(quinolin-8-yl)propanamide (8c): Following the general procedure, **8c** was obtained after purification by column chromatography on silica gel (EtOAc:Hexane = 20:80) as a brown colour semi solid (44 mg, 47%); R_f = 0.6 (EtOAc:Hexane = 20:80); mp 184 – 186 ^oC; FTIR (DCM): 3341, 3094, 1677, 1577 and 1522 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 9.80 (s, 1H), 8.79 – 8.78 (m, 2H), 8.17 (d, 1H, *J* = 8.2 Hz), 7.91 (d, 2H, *J* = 8 Hz), 7.55 – 7.53 (m, 2H), 7.46 (dd, 1H, J_1 = 8.2 Hz, J_2 = 4.2 Hz), 7.41 (d, 2H, *J* = 8 Hz), 3.22 (t, 2H, *J* = 7.8 Hz), 2.93 (t, 2H, *J* = 7.6 Hz), 2.58 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 197.9,



8c

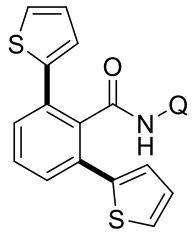
170.2, 148.1, 146.6, 138.2, 136.4, 135.4, 134.3, 128.7, 128.7, 127.9, 127.4, 121.7, 121.6, 116.5, 39.0, 31.3, 26.6; HRMS (ESI): MH^+, found 319.1456 $C_{20}H_{19}N_2O_2$ requires 319.1447.

3.2.13. 3-(4-Methoxyphenyl)-*N*-(quinolin-8-yl)hexadecanamide (9b): Following the general procedure, **9b** was obtained after purification by column chromatography on silica gel (EtOAc:Hexane = 20:80) as a brown colour semi solid (105 mg, 72%); R_f = 0.6 (EtOAc:Hexane = 20:80); FTIR (DCM): 3353, 2923, 1688, 1525 and 1483 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 9.67 (s, 1H), 8.78 – 8.74 (m, 2H), 8.15 (d, 1H, J = 8.2 Hz), 7.54 – 7.47 (m, 2H), 7.45 (dd, 1H, J_1 = 8.2, J_2 = 4.2 Hz), 7.23 (d, 2H, J = 8.3 Hz), 6.84 (d, 2H, J = 8.3 Hz), 3.76 (s, 3H), 3.28 – 3.24 (m, 1H), 2.85 – 2.81 (m, 2H), 1.79 – 1.65 (m, 2H), 1.28 – 1.22 (m, 22H), 0.92 – 0.88 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.7, 158.0, 148.0, 138.3, 136.4, 136.3, 134.4, 128.4, 127.9, 127.4, 121.5, 121.4, 116.5, 113.9, 55.1, 46.2, 41.9, 36.4, 31.9, 29.7, 29.7, 29.6, 29.6, 29.5, 29.4, 27.4, 24.8, 22.7, 14.2; HRMS (ESI): MH^+, found 489.3503 $C_{32}H_{45}N_2O_2$ requires 489.3481.



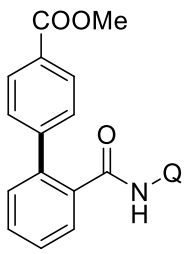
9b

3.2.14. *N*-(Quinolin-8-yl)-2,6-di(thiophen-2-yl)benzamide (10b): Following the general procedure, **10c** was obtained after purification by column chromatography on silica gel (EtOAc:Hexane = 20:80) as a colourless solid (55 mg, 45%); R_f = 0.6 (EtOAc:Hexane = 20:80); mp 184 – 186 ^oC; FTIR (DCM): 3341, 3094, 1677, 1577 and 1522 cm^{-1}; HRMS (ESI): ^1H NMR (400 MHz, $CDCl_3$): δ 9.88 (s, 1H), 8.78 (d, 1H, J = 7.1 Hz), 8.66 (d, 1H, J = 3.5 Hz), 8.11 (d, 1H, J = 8.2 Hz), 7.60 – 7.49 (m, 5H), 7.38 (dd, 1H, J_1 = 8.2 Hz, J_2 = 4.1 Hz), 7.35 – 7.34 (m, 2H), 7.22 (d, 2H, J = 4.9 Hz), 6.93 – 6.91 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 167.3, 148.1, 140.9, 138.4, 136.1, 135.7, 134.3, 133.0, 130.0, 129.4, 127.8, 127.6, 127.3, 127.1, 126.2, 121.9, 121.5, 116.8; MH^+, found 413.0764 $C_{24}H_{17}N_2OS_2$ requires 413.0782.



10b

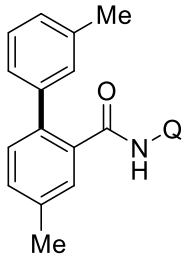
3.2.15. Methyl 2'-(quinolin-8-ylcarbamoyl)-[1,1'-biphenyl]-4-carboxylate (10f′): Following the general procedure, **10g′** was obtained after purification by column chromatography on silica gel (EtOAc:Hexane = 20:80) as a colourless solid (63 mg, 55%); R_f = 0.4 (EtOAc:Hexane = 20:80); mp 148 – 150 ^oC; FTIR (DCM): 3337, 1722, 1672, 1596 and 1524 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 9.84 (s, 1H), 8.81 (dd, 1H, J_1 = 7.4 Hz, J_2 = 1.2 Hz), 8.55 (dd, 1H, J_1 = 4.2 Hz, J_2 = 1.6 Hz), 8.10 (dd, 1H, J_1 = 8.2 Hz, J_2 = 1.4 Hz), 7.99 (d, 2H, J = 8.3



10f'

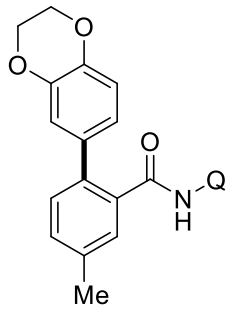
Hz), 7.94 (dd, 1H, J_1 = 7.4 Hz, J_2 = 1.2 Hz), 7.63 – 7.48 (m, 7H), 7.36 (dd, 1H, J_1 = 8.2 Hz, J_2 = 4.2 Hz), 3.85 (s, 3H); ^{13}C NMR (100 MHz, CDCl3): 167.4, 166.8, 147.9, 144.9, 139.3, 138.4, 136.2, 136.1, 134.4, 130.7, 130.6, 129.7, 129.2, 129.2, 129.0, 128.3, 127.8, 127.3, 121.8, 121.5, 116.4, 52.1; HRMS (ESI): MH^+, found 383.1379 $C_{24}H_{19}N_2O_3$ requires 383.1396.

3.2.16. 3',4-Dimethyl-*N*-(quinolin-8-yl)-[1,1'-biphenyl]-2-carboxamide (11a): Following the general procedure, **11a** was obtained after purification by column chromatography on silica gel (EtOAc:Hexane = 20:80) as a colourless solid (105 mg, 60%); R_f = 0.6 (EtOAc:Hexane = 20:80); mp 130 – 131^{o}C; FTIR (DCM): 3312, 3051, 1658, 1526 and 1430 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.77 (s, 1H), 8.84 (d, 1H, J = 7.5 Hz), 8.54 (d, 1H, J = 4.0 Hz), 8.09 (d, 1H, J = 8.24 Hz), 7.74 (s, 1H), 7.54 – 7.45 (m, 2H), 7.39 – 7.35 (m, 4H), 7.31 – 7.28 (m, 1H), 7.14 (t, 1H, J = 7.6 Hz), 6.96 (d, 1H, J = 7.5 Hz), 2.50 (s, 3H), 2.26 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 168.2, 147.7, 139.9, 138.4, 138.0, 137.6, 137.4, 136.0, 135.9, 134.7, 131.3, 130.6, 129.7, 128.2, 128.1, 127.7, 127.3, 126.1, 121.4, 121.4, 116.2, 21.4, 21.1; HRMS (ESI): MH^+, found 353.1664 $C_{24}H_{21}N_2O$ requires 353.1654.



11a

3.2.17. 2-(2,3-Dihydrobenzo[*b*][1,4]dioxin-6-yl)-5-methyl-*N*-(quinolin-8-yl)benzamide (11c) : Following the general procedure, 11c was obtained after purification by column chromatography on silica gel (EtOAc:Hexane = 20:80) as a colourless solid (104 mg, 53%); R_f = 0.4 (EtOAc:Hexane = 20:80); mp 174 – 176 ^{o}C; FTIR (DCM): 3328, 1660, 1581, 1525 and 1484 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.85 (s, 1H), 8.86 (d, 1H, J = 7.5 Hz), 8.62 – 8.61 (m, 1H), 8.09 (d, 1H, J = 8.2 Hz), 7.73 (s, 1H), 7.57 – 7.53 (m, 1H), 7.48 – 7.46 (m, 1H), 7.39 – 7.36 (m, 3H), 7.08 (s, 1H), 6.97 (d, 1H, J = 8.3 Hz), 6.76 (dd, 1H, J_1 = 8.2 Hz, J_2 = 1.8 Hz), 4.10 (s, 4H), 2.48 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): 168.1, 147.7, 143.5, 143.2, 138.5, 137.3, 136.9, 136.0, 135.7, 134.7, 133.4, 131.3, 130.5, 129.8, 127.7, 127.4, 122.3, 121.4, 121.3, 117.9, 117.2, 116.3, 64.3, 64.2, 21.1; HRMS (ESI): MH^+, found 397.1534 $C_{25}H_{21}N_2O_3$ requires 397.1552.



11c

3.3. Synthesis of palladium complex 18 from 2-methylbenzoic anhydride (2j) and synthesis of arylated carboxamide 11e from 18: A mixture of 2-methylbenzoic anhydride **(2j**, 0.7 mmol) and 8 -aminoquinoline (0.7 mmol) in anhydrous toluene (4 mL) was heated at 100 ^{o}C for 30 h. Then, the solvent was evaporated under reduced pressure and the crude reaction mixture was purified by column chromatography to afford 2-methyl-*N*-(quinolin-8-

yl)benzamide (**1cj**) in 63% yield. Next, a mixture of 2-methyl-*N*-(quinolin-8-yl)benzamide (**1cj**, 0.43 mmol) and $Pd(OAc)_2$ (0.43 mmol) in anhydrous MeCN (3 mL) was stirred at 60 ^oC for 4 h. The reaction mixture was cooled to rt, the resulting yellowish precipitate was collected by filtration, washed with 5 mL of MeCN and then solid was re-dissolved in 10-15 mL CH_2Cl_2, and concentrated under reduced pressure to give the palladium complex **18** in 42% yield (the work up procedure reported in ref.[9b] was followed to isolate **18**). **18**: mp 230-232 ^oC (decomposed); ^1H NMR (DMSO-d_6, 400 MHz, ppm): δ 9.18 (br. s, 1H), 9.02 (d, 1H, *J* = 7.4 Hz), 8.47 (d, 1H, *J* = 8.0 Hz,), 7.62-59 (m, 1H), 7.48 (t, 1H, , *J* = 7.8 Hz), 7.41 (d, 1H, , *J* = 7.6 Hz), 6.98– 6.91 (m, 2H), 6.85 (d, 1H, *J* = 6.6 Hz), 2.54 (s, 3 H), 2.03 (s, 3H); ^{13}C NMR (DMSO-d_6, 101 MHz, ppm) δ 177.7, 150.0, 147.4, 146.9, 145.3, 143.7, 139.7, 130.9, 130.3, 129.5, 129.1, 128.9, 122.0, 119.5, 119.0, 118.5, 20.2, 1.6; MS (ASAP) *m/z* 245 $[M]^+$ - (Pd+MeCN+CH_3). A mixture of palladium complex **18** (0.08 mmol) and 4–iodoanisole (0.40 mmol) in acetone (1.0 mL) was stirred at rt 74 h and then refluxed at 45 ^oC for 24 h. Then, the reaction mixture was diluted with dichloromethane (2 mL) followed by addition of an excess of aqueous HI (1 mL). The resulting solution was stirred for an hour and basified by solid $NaHCO_3$. Then, extracted with dichloromethane (3 x 10 mL) and the combined organic layers were dried over anhydrous Na_2SO_4. Evaporation of solvent under reduced pressure afforded a crude mixture, which was purified by column chromatography (hexane/EtOAc= 60:40) to afford the arylated product **11e**[7e] in 44% yield.

References and notes

1. For selected reviews dealing with the sp^2/sp^3 C-H activation reactions, see: (a) Kakiuchi, F.; Murai, S. *Acc. Chem. Res.* **2002**, *35*, 826; (b) Lyons, T. W.; Sanford, M. S. *Chem. Rev.* **2010**, *110,* 1147; (c) Hirano, K.; Miura, M. *Chem. Lett.* **2015**, *44*, 868; (d) Banerjee, A.; Sarkar S.; Patel, B. *Org. Biomol. Chem.* **2017**, *15*, 505; (e) Ackermann, L. *Acc. Chem. Res.* **2014**, *47*, 281; (f) Rajesh, N.; Barsu N.; Sundararaju, B. *Tetrahedron Lett.* **2018**, *59*, 862; (g) Ping, Y.; Wang, L.; Ding, Q.; Peng, Y. *Adv. Synth. Catal.* **2017**, *359*, 3274; (h) Yang, Y.; Lan J.; You, J. *Chem. Rev.* **2017**, *117*, 8787; (i) Bag S.; Maiti, D. *Synthesis* **2016**, *48*, 804; (j) Subramanian, P.; Rudolf, G. C.; Kaliappan, K. P. *Chem. Eur. J.* **2016,** *11*, 168; (k) Neufeldt, S. R.; Sanford, M. S. *Acc. Chem. Res.* **2012,** *45*, 936; (l) Giri, R.; Thapa, S.; Kafle, A. *Adv. Synth. Catal.* **2014,** *356*, 1395; (m) Zhang, Q.; Chen, K.; Shi, B.-F. *Synlett* **2014**, *25*, 1941; (n) Baudoin, O. *Acc. Chem. Res.* **2017**, *50*, 1114; (o) Chu, J. C. K.; Rovis, T. *Angew. Chem. Int. Ed.* **2018**, *57*, 62; (p) St John-Campbell, S.; Bull. J. A. *Org. Biomol. Chem.* **2018**, *16*, 4582; (q) Sun, H.; Guimond N.;

Huang, Y. *Org. Biomol. Chem.* **2016**, *14*, 8389; (r) Hui C.; Xu, J. *Tetrahedron Lett.* **2016**, *57*, 2692.

2. For selected reviews dealing with the reusable bidentate DG-assisted sp^3 C-H functionalization/arylation, see: (a) Daugulis, O.; Do, H.-Q.; Shabashov, D. *Acc. Chem. Res.* **2009**, *42*, 1074; (b) Li, H.; Li, B.-J.; Shi, Z.-J. *Catal. Sci. Technol.* **2011**, *1*, 191; (c) Rouquet G.; Chatani, N. *Angew. Chem. Int. Ed.* **2013**, *52*, 11726; (d) Corbet, M.; De Campo, F. *Angew. Chem. Int. Ed.* **2013**, *52*, 9896; (e) Daugulis, O.; Roane, J.; Tran, L. D. *Acc. Chem. Res.* **2015**, *48*, 1053; (f) Qiu, G.; Wu, J. *Org. Chem. Front.* **2015**, *2*, 136; (g) Zhang, B.; Guan H.; Shi, B.-F. *Chin. J. Org. Chem.* **2014**, *34*, 1487; (h) Rit, R. K.; Yadav, M. R.; Ghosh, K.; Sahoo, A. K. *Tetrahedron* **2015**, *71*, 4450; (i) Castro, L. C. M.; Chatani, N. *Chem. Lett*. **2015**, *44*, 410; (j) Yadav, M. R.; Rit, R. K.; Majji, S.; Sahoo, A. K. *Asian. J. Org. Chem.* **2015**, *4*, 846; (k) Yang, X.; Shan, G.; Wang, L.; Rao, Y. *Tetrahedron. Lett*. **2016**, *57*, 819; (l) Liu, J.; Chen G.; Tan, Z. *Adv. Synth. Catal.* **2016**, *358*, 1174; (m) He, G.; Wang, B.; Nack W. A.; Chen, G. *Acc. Chem. Res.* **2016**, *49*, 635; (n) He, J.; Wasa, M.; Chan, K. S. L.; Shao Q.; Yu, J.-Q. *Chem. Rev.* **2017**, *117*, 8754; (o) Sambiagio, C.; Schonbauer, D.; Blieck, R.; Dao-Huy, T.; Pototschnig, G.; Schaaf, P.; Wiesinger, T.; Zia, M. F.; Wencel-Delord, J.; Besset, T.; Maes, B. U. W.; Schnürch, M. *Chem. Soc. Rev.* **2018**, 47, 6603.

3. For selected articles dealing with bidentate DG-assisted sp^3 C-H arylation/alkylation of carboxamides, see: (a) Zaitsev, V. G.; Shabashov, D.; Daugulis, O. *J. Am. Chem. Soc.* **2005**, *127*, 13154; (b) Shabashov, D.; Daugulis, O. *J. Am. Chem. Soc.* **2010**, *132*, 3965; (c) Hoshiya, N.; Kondo, M.; Fukuda, H.; Arisawa, M.; Uenishi J.; Shuto, S. *J. Org. Chem.* **2017**, *82*, 2535; (d) Aihara, Y.; Chatani, N. *J. Am. Chem. Soc.* **2014**, *136*, 898; (e) Tang, H.; Huang, X.-R.; Yao, J.; Chen, H. *J. Org. Chem.* **2015**, *80*, 4672; (f) Graczyk, K.; Haven, T.; Ackermann, L. *Chem. Eur. J.* **2015**, *21*, 8812; (g) Zhang, Y.- F.; Zhao, H.-W.; Wang, H.; Wei, J.-B.; Shi, Z.-J. *Angew. Chem. Int. Ed.* **2015**, *54*, 13686; (h) Zhang, S.-J.; Sun, W.-W.; Yu, Q.-Y.; Cao, P.; Dong, X.-P.; Wu, B. *Tetrahedron Lett.* **2017**, *58*, 606; (i) Zhang, F.-L.; Hong, K.; Li, T.-J.; Park, H.; Yu, J.-Q. *Science* **2016**, *351*, 252; (j) Chen, G.; Gong, W.; Zhuang, Z.; Andrä, M. S.; Chen, Y.-Q.; Hong, X.; Yang, Y.-F.; Liu, T.; Houk, K. N.; Yu, J.-Q. *Science* **2016**, *353*, 1023; (k) Yan, X.; Long, R.; Luo, F.; Yang, L.; Zhouo, X. *Tetrahedron Lett.* **2017**, *58*, 54; (l) Maetani, M.; Zollere, J.; Melillo, B.; Verho, O.; Kato, N.; Pu, J.; Comer, E.; Schreiber, S. L. *J. Am. Chem. Soc.* **2017**, *139*, 11300; (m) Liu, J.; Xie, Y.; Zeng, W.; Lin, D.; Deng Y.; Lu, X. *J. Org. Chem.* **2015**, *80*, 4618; (n) Reddy, B. V. S.; Reddy, L. R.; Corey, E. J. *Org. Lett.*

2006, *8*, 3391; (o) Mu, D.; Gao, F.; Chen G.; He, G. *ACS Catal.* **2017**, *7*, 1880; (p) Luo, F.; Yang, J.; Li, Z.; Xiang, H.; Zhou, X. *Adv. Synth. Catal.* **2016**, *358*, 887; (q) He, G.; Zhang, S.-Y.; Nack, W. A.; Li, Q.; Chen, G. *Angew. Chem. Int. Ed.* **2013**, *52*, 11124; (r) Gutekunst, W. R.; Gianatassio, R.; Baran, P. S. *Angew. Chem. Int. Ed.* **2012**, *51*, 7507; (s) Zhang, Q.; Yin, X.-S.; Zhao, S.; Fang, S.-L.; Shi, B.-F. *Chem. Commun.* **2014**, *50*, 8353; (t) Affron, D. P.; Bull, J. A. *Eur. J. Org. Chem.* **2016**, 139; (u) Gou, Q.; Zhang, Z.-F.; Liu, Z.-C.; Qin, J. *J. Org. Chem.* **2015**, *80,* 3176; (v) Yan, S.-B.; Zhang, S.; Duan, W.-L. *Org. Lett.* **2015**, *17,* 2458.

4. For available articles dealing with multicomponent reaction-based sp^3 C-H functionalization using acid chlorides and in situ installation of the DG, 8-aminoquinoline, see: (a) Mohan, S.; Gopalakrishnan B.; Babu, S. A. *Tetrahedron* **2016**, *72*, 5853; (b) **Liu, Y.;** Zhang, Y.; Huang, M.; Wan, J.-P. *RSC Adv.* **2015**, *5*, 46192; (c) Liu, Y.; Zhang, Y.; Cao X.; Wan, J.-P. *Beilstein J. Org. Chem.* **2016**, *12*, 1122; (d) For a selected review dealing with multicomponent reaction-based sp^3/sp^2 C–H bond functionalization, see: Wan, J.-P.; Gan L.; Liu, L. *Org. Biomol. Chem.* **2017**, *15*, 9031.
5. For selected articles of our group dealing with the bidentate DG-assisted sp^3 C-H arylation of carboxamides, see: (a) Gopalakrishnan, B.; Mohan, S.; Parella, R.; Babu, S. A. *J. Org. Chem.* **2016**, *81*, 8988; (b) Gopalakrishnan, B.; Babu, S. A.; Padmavathi, R. *Tetrahedron* **2015**, *71*, 8333; (c) Reddy, C.; Bisht, N.; Parella R.; S. A. Babu, *J. Org. Chem.* **2016**, *81*, 12143; (d) Parella R.; Babu, S. A. *J. Org. Chem.* **2017**, *82*, 7123 and references cited therein; (e) see ref.[4a]
6. For a recent paper dealing with the DG-assisted Pd(II)-catalyzed sp^3 C-H functionalization of carboxamides using CsOAc as an additive instead of Ag salt, see: Gou, Q.; Liu, G.; Zhou, L.; Chen S.; Quin, J. *Eur. J. Org. Chem.* **2017**, 6314 and references cited therein.
7. For articles dealing with the bidentate DG-assisted sp^3/sp^2 C-H arylation of carboxamides and reported the synthesis and characterization data of some of the compounds discussed in this paper, see: (a) Pan, F.; Shen, P.-X.; Zhang, L.-S.; Wang X.; Shi, Z.-J. *Org. Lett.* **2013**, *15*, 4758; (b) Wei, Y.; Tang, H.; Cong, X.; Rao, B.; Wu, C.; Zheng, X. *Org. Lett.* **2014**, *16*, 2248; (c) Reddy, M. D.; Blanton A. N.; Watkins, E. B. *J. Org. Chem.* **2017**, *82*, 5080; (d) Shang, R.; Ilies, L.; Asako, S.; Nakamura, E. *J. Am. Chem. Soc.* **2014**, *136*, 14349; (e) Ilies, L.; Matsubara, T.; Ichikawa, S.; Asako, S.; Nakamura, E. *J. Am. Chem. Soc.* **2014**, *136*, 13126; (f) Tran, L. D.; Popov, I.; Daugulis, O. *J. Am. Chem. Soc.* **2012**, *134*, 18237.

8. (a) Y. Wang, W. Ren, Y. Shi, *Org. Biomol. Chem.*, 2015, **13**, 8416; (b) Wang, Y.; Zeng, Y.; Yang, B.; Shi, Y. *Org. Chem. Front.* **2016**, *3*, 1131; (c) Liu, Y.; Zhang Y.; Wan, J.-P. *J. Org. Chem.* **2017**, *82*, 8950; (d) Yokota, A.; Aihara Y.; Chatani, N. *J. Org. Chem.* **2014**, *79*, 11922.
9. For selected references revealing the mechanism for the Pd(II)-catalyzed, 8-aminoquinoline-assisted *β*-C-H activation of carboxamides, see: (a) Successful isolation of Pd(II) intermediate after the sp^3 *β*-C-H activation of carboxamide, see ref.[3b]; (b) Successful isolation of Pd(II) intermediate after the sp^2 *β*-C-H activation of carboxamide, Zhang, S.-Y.; Li, Q.; He, G.; Nack, W. A.; Chen, G. *J. Am. Chem. Soc.* **2015**, *137*, 531.
10. It is to be noted that the mechanism represented in Scheme 5 is well established in the literature and supported by the studies carried out by various research groups.[2] For example, Daugulis et al have isolated the Pd(II) intermediate **19** after the sp^3 *β*-C-H activation from the corresponding carboxamide.[3b] Similarly, Chen et al have isolated the Pd(II) intermediate **20** after the sp^2 *β*-C-H activation from the corresponding carboxamide.[9b] While this paper aims to improve the existing two-step Pd(II)-catalyzed *β*-C-H arylation of carboxamides as a single-step method and multicomponent-type reaction comprising involving anhydride as substrate (**2**) *via* in situ installation of bidentate DG. Based on the suggestion of the Reviewer(s) we also intended to isolate a Pd(II) intermediate from our reactions and out of various trials we could isolate the Pd(II) intermediate **18** from the reaction of **1cj** with the $Pd(OAc)_2$ catalyst by following the procedure reported by Chen et al for the synthesis of **20**. The Pd(II) intermediate **18** was characterized by the NMR and mass analysis. The NMR pattern of the Pd(II) intermediate **18** was similar to the Pd(II) intermediate **20**. Characteristically, in the ^{13}C NMR, the methyl signal of acetonitrile moiety of the complex **18** appeared at δ 1.6 ppm as observed for the Pd(II) intermediate **20**.[9b] Further, mass analysis (by ASAP method from QTOF mass analyzer) of the Pd(II) intermediate **18** revealed a characteristic and prominent mass value of *m/z* 245 for the possible fragment corresponding to $[M]^+$ - ($Pd+MeCN+CH_3$). Our efforts to obtain a single crystal for X-ray analysis are not fruitful at this stage and will be reported in the near future after we succeed in getting a suitable single crystal for analysis. However, treatment of the isolated Pd(II) intermediate **18** with 4-idonoanisole gave the sp^2 *β*-C-H arylated product **11e** in 44% yield (Scheme 5), which is in accordance with the mechanism represented in the literature.

Chapter 3

Assembling of Polyaryls (Terphenyls, Tetraphenyls, Pentaphenyls and Hexaphenyls) *via* The Pd(II)-catalyzed C-H Arylation of Biaryl Carboxamides with Iodobiaryls.

For the purpose of this Thesis work, the work of Chapter 3 is re-used (adapted) with permission from (Dalal A.; Babu, S.A*.; Banga, S. *Asian J. Org. Chem.* **2023**, e202300508 (https://doi.org/10.1002/ajoc.202300508). Title; Assembling of Polyaryls (Terphenyls, Tetraphenyls, Pentaphenyls and Hexaphenyls) *via* The Pd(II)-catalyzed C-H Arylation of Biaryl Carboxamides with Iodobiaryls.

The transition metal-catalyzed cross-coupling reactions are fundamental C-C bond-forming methods and are extensively utilized in the synthesis of natural products, pharmaceuticals, bio-active compounds, functional materials, etc.[1] Especially, the synthesis of biaryl-based scaffolds has received significant attention. Biaryl-based compounds are privileged scaffolds, present in a number of drug molecules, natural products, bio-active synthetic compounds, and organic functional materials.[1,2]

Along this line, various polyaryl molecules (π-extended biaryls or polyphenylenes) such as teraryls (terphenyls), quateraryls (quaterphenyls), penta-aryls (pentaphenyls), hexa-aryls (hexaphenyls), etc have received considerable attention in organic, materials and medicinal chemistry research areas (e.g., **1a-l**, Figure 1).[2-6] Such compounds have found various applications as biologically or medicinally active compounds, precursors of functional materials including organic field-effect transistors (OFETs), organic light-emitting diodes (OLEDs) and organic solar cells (OSCs), etc.[2-6]

Various catalytic aryl-aryl cross-coupling protocols involving organometallic reagents have been established for assembling polyaryl or polyphenylene compounds (π-extended biaryl motifs).[3,5,6] While the cross-coupling methods are efficient for assembling the π-extended biaryl motifs (polyaryls), however, the traditional cross-coupling protocols are associated with unavoidable limitations (e.g., availability and the requirement of pre-assembling of organometallic reagents, Scheme 1). Sometimes such a limitation is a hurdle for the elaboration of the substrate scope in the investigations pertaining to aryl-aryl cross-coupling reactions affording the π-extended biaryl compounds (e.g., **2c,e,j,l,q,u,z**, Scheme 1).

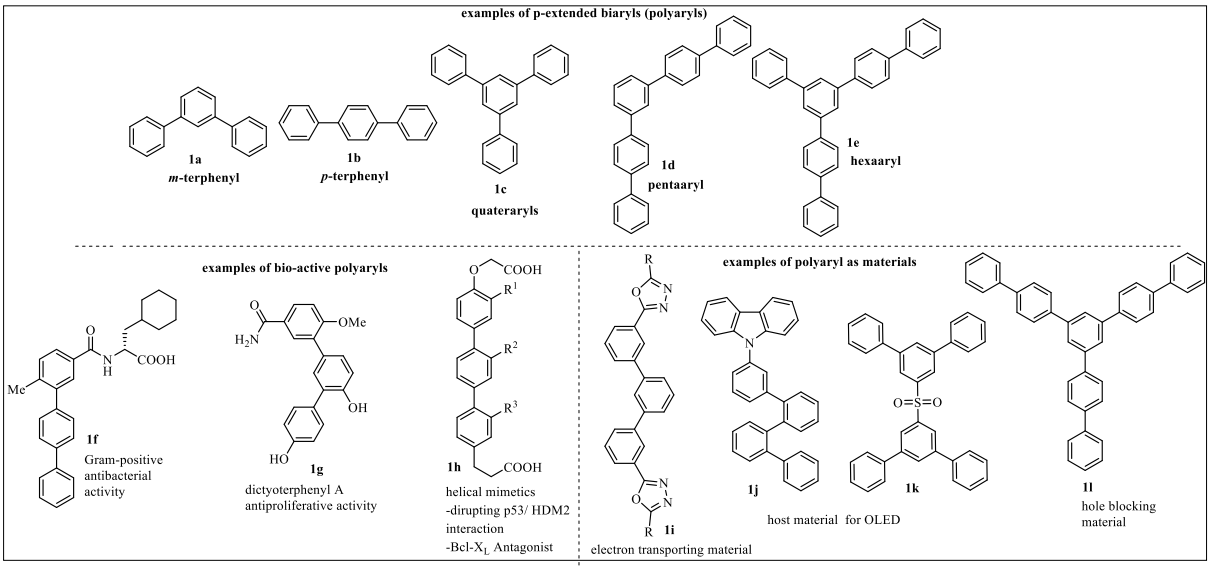


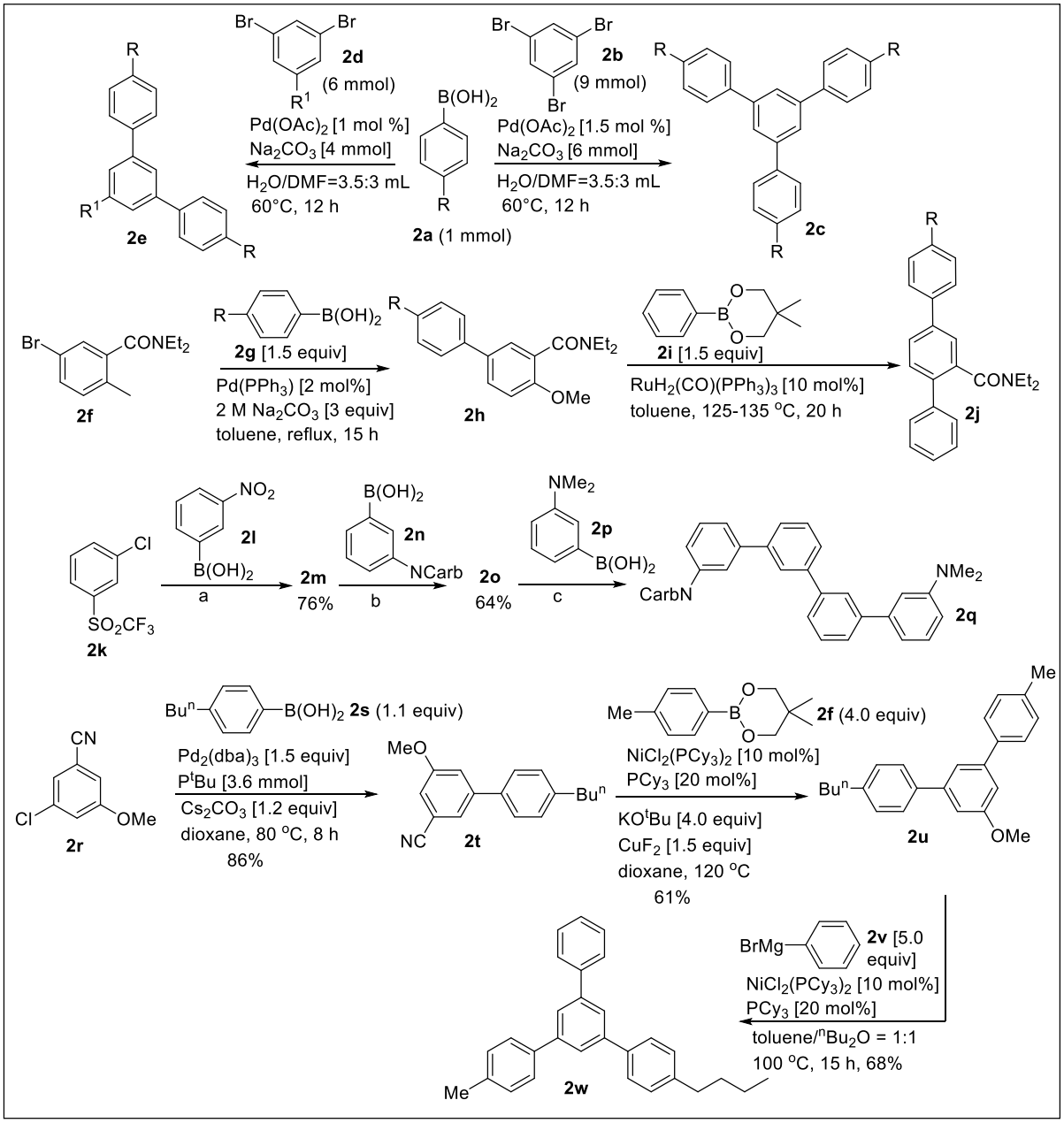
Figure 1. Examples of π-extended biaryls (polyaryls) and bioactive polyaryls.

In recent years, the transition metal-catalyzed functionalization of the C-H bonds of small molecules has proved to be a versatile method in organic synthesis.[7,8] The C-H functionalization tactic enables quick assembling of a wide range of targets of functionalized small organic molecules.[7,8] Of particular interest, the Pd(II)-catalyzed bidentate directing group (DG)-aided C-H functionalization of aliphatic and aromatic carboxamides has received significant attention for assembling functionalized aromatic, alicyclic- and aliphatic compounds.[8-10]

Markedly, the C-H functionalization method has also been extensively used for performing the aryl-aryl coupling for assembling various biaryls and polyaryls.[7,8,11-14] In particular, we aimed to extend the applicability of the Pd(II)-catalyzed bidentate DG-aided, site-selective *ortho* C-H arylation method for constructing the π-extended biaryl (polyaryl) motifs using biaryl-based carboxamides and iodobiaryls as the coupling partners in a single operation (Scheme 2). The current investigation on the bidentate DG-aided C-H arylation of biaryl carboxamides with iodobiaryls is expected to serve as a useful route to enrich the library of the π-extended biaryl (polyaryl) motifs.

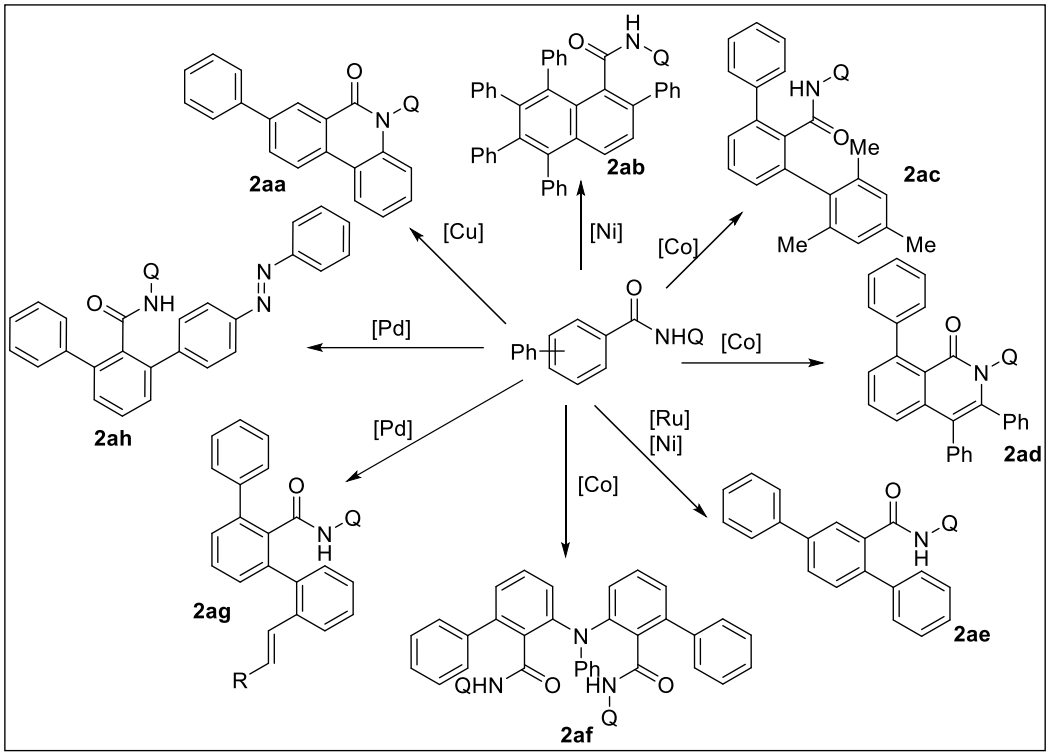
Nevertheless, there have been a few instances of C-H functionalization of biaryl-based carboxamides affording the π-extended biaryls or polyaryls (Scheme 2a).[15] Niu and Song showed[15a] the synthesis of two examples of triaryl amines *via* Co-catalyzed C-H/N-H coupling. Sunnam/Belani showed the synthesis of two examples of terphenyls *via* Pd(II)-catalyzed C-H arylation using an aryne.[15b] Ackermann reported the synthesis of an example of terphenyl *via* cobalt-catalyzed C-H arylation using an aryl siloxane.[15c] Chatani reported the synthesis of two examples of terphenyls *via* Ni or Ru-catalyzed C-H arylation using PhI or

PhBr.[15d,e] Chatani and Huang independently reported the synthesis of tetrasubstituted naphthamides *via* Ni-catalyzed C-H activation/alkyne insertion reactions.[15f,g] Jeganmohan reported the synthesis of an example of isoquinolone *via* cobalt-catalyzed C-H/N-H annulation.[15h] We recently reported the synthesis of a few examples of modified azobenzenes *via* Pd-catalyzed C-H arylation of biaryl-based carboxamides with iodoazobenzene.[15i] Zhang reported the synthesis of an example of phenanthridinone *via* Cu-catalyzed C-H/N-H annulation.[15j]



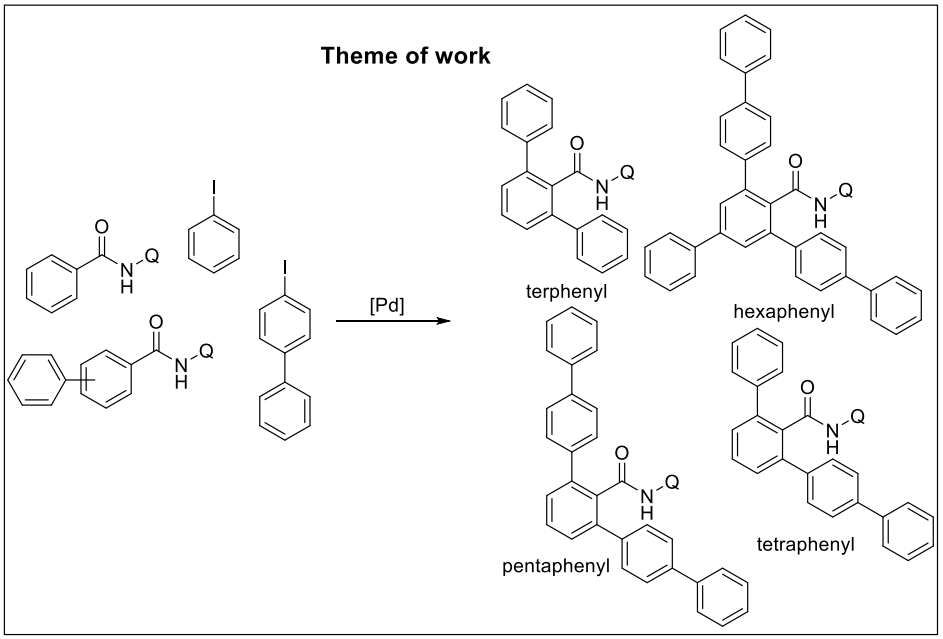
a: $Pd(OAc)_2$ (1 mol%), XPhos (3 mol%),K_3PO_4 (3 equiv), THF, 22 °C, 17 h; b: standard conditions; c: $Pd(acac)_2$ (5 mol%), Brett Phos (20 mol%), 18-crown-6 (10 mol%), K_3PO_4 (3 equiv), dioxane, 130 °C, 48 h. NCarb = N-carbazole.

Scheme 1. The conventional routes toward polyaryls.[3,5,6]



Scheme 2a. Examples of C-H functionalization using biaryl carboxamides.[15]

While the bidentate DG-aided C-H arylation of aromatic carboxamides has been well documented, however, the assembling of polyaryl molecules especially, quaterphenyls, pentaphenyls, hexaphenyls using biaryl-based carboxamides and iodobiaryls as the coupling partners has not been explored well.[7,8,12-15] Given that various π-extended biaryls (polyaryls including teraryls, quateraryls, etc) have received significance as biologically active compounds, precursors of molecular devices and functional materials (Figure 1). The current investigation intends to expand the C-H arylation tactic-based aryl-aryl coupling method by coupling various biaryl-based carboxamides with iodobiaryls and to obtain a wide range of the π-extended biaryl (polyaryls) compounds (Scheme 2b).

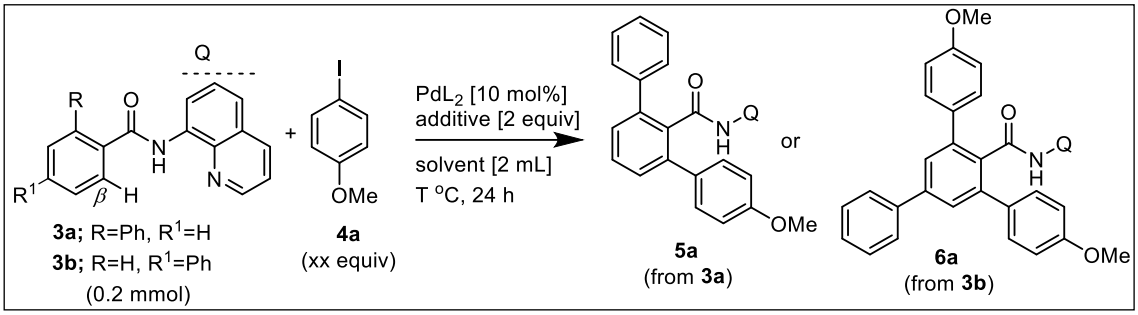


Scheme 2b. Assembling of polyaryls *via* C-H arylation of biaryl carboxamides.

Results and Discussion

To commence assembling the π-extended biaryls, initially, we carried out the *β*-C-H (*ortho*) arylation of biaryl carboxamide **3a** with iodobiaryl **4a** by using the standard conditions of bidentate DG-assisted Pd(II) catalyzed C-H arylation reaction.[8,9] Table 1 shows a few screenings of reaction conditions comprising of the Pd(II)-catalyzed *β*-C-H (*ortho*) arylation of biaryl carboxamide **3a** possessing the 8-aminoquionline directing group with *p*-anisyl iodide (**4a**). A silver salt (e.g., AgOAc, Ag_2CO_3) or an alkali metal-based salt (e.g., K_2CO_3, CsOAc, Cs_2CO_3) is generally employed as the halide ion scavenger and this additive is believed to help in regenerating the Pd(II) catalyst in the proposed bidentate DG-assisted Pd^{II}-Pd^{IV} catalytic cycle.[8,9a]

Table 1. Synthesis of terphenyl derivative **5a** and tetraphenyl derivative **6a** from C-H arylation of biaryl carboxamides **3a,b** with **4a**



entry	PdL_2	4a (equiv)	Additive	Solvent	T (°C)	yield (%)
1[a]	$Pd(OAc)_2$	4	AgOAc	toluene	110	5a: 48
2[a]	$Pd(OAc)_2$	4	K_2CO_3	toluene	110	5a: 67
3[a]	$Pd(OAc)_2$	4	K_2CO_3	*o*-Xylene	130 [12 h]	5a: 60
4[a]	$Pd(OAc)_2$	4	AgOAc	*o*-Xylene	130	5a: 67
5[a]	$Pd(OAc)_2$	4	Cs_2CO_3	*o*-Xylene	130	5a: 68
6[a]	$Pd(OAc)_2$	4	CsOAc	*o*-Xylene	130	5a: 30
7[a]	$Pd(OAc)_2$ (5 mol%)	4	K_2CO_3	*o*-Xylene	130	5a: 53
8[a]	$Pd(TFA)_2$	4	K_2CO_3	*o*-Xylene	130	5a: 84
9[a]	$Pd(MeCN)_2Cl_2$	4	K_2CO_3	*o*-Xylene	130	5a: 80
10[a]	**$Pd(OAc)_2$**	**4**	**K_2CO_3**	***o*-Xylene**	**130**	**5a: 88**
11[b]	$Pd(OAc)_2$	1	K_2CO_3	*o*-Xylene	130	6a: 23
12[b]	$Pd(OAc)_2$	2	K_2CO_3	*o*-Xylene	130	6a: 36
13[b]	$Pd(OAc)_2$	3	K_2CO_3	*o*-Xylene	130	6a: 72
14[b]	**$Pd(OAc)_2$**	**4**	**K_2CO_3**	***o*-Xylene**	**130**	**6a: 80**
15[b]	$Pd(OAc)_2$	4	AgOAc	*o*-Xylene	130	6a: 60

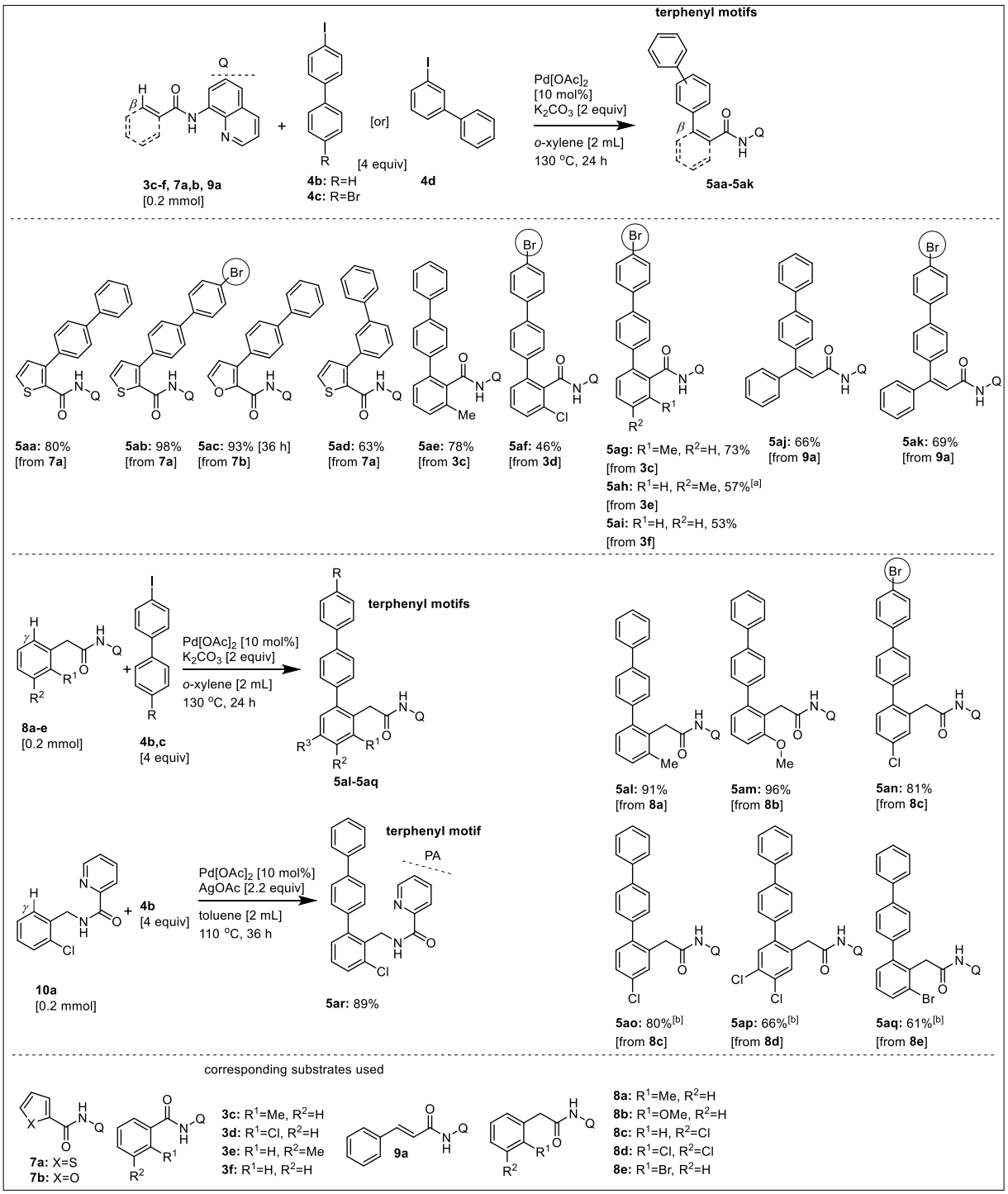
[a]**3a** is used, [b]**3b** is used

Heating the biaryl carboxamide **3a** with **4a** in the presence of the $Pd(OAc)_2$ catalyst (10 mol%) and AgOAc or K_2CO_3 as an additive in toluene at 110 °C for 24 h afforded the terphenyl derivative **5a** in satisfactory yield (48-67%, entries 1,2, Table 1). Heating substrate **3a** with **4a** in the presence of the $Pd(OAc)_2$ catalyst (10 mol%) and K_2CO_3 in *o*-xylene at 130 °C for 12 h afforded **5a** in 60% yield (entry 3, Table 1). Heating substrate **3a** with **4a** in the presence of the $Pd(OAc)_2$ catalyst (10 mol%) and AgOAc or Cs_2CO_3 or CsOAc as an additive in *o*-xylene at 130 °C for 24 h afforded **5a** in low to moderate yield (30-68%, entries 4-6, Table 1). Heating substrate **3a** with **4a** in the presence of the $Pd(OAc)_2$ catalyst (5 mol%) and K_2CO_3 in *o*-xylene

at 130 °C for 24 h afforded **5a** in 53% yield (entry 7, Table 1). Heating substrate **3a** with **4a** in the presence of $Pd(TFA)_2$ or $Pd(MeCN)_2Cl_2$ or $Pd(OAc)_2$ as the catalyst (10 mol%) and K_2CO_3 as an additive in *o*-xylene at 130 °C for 24 h afforded **5a** in good yields (80-88%, entries 8-10, Table 1).

Subsequently, we treated the biaryl carboxamide **3b** with aryl iodide **4a** (1-4 equiv) in the presence of the $Pd(OAc)_2$ catalyst (10 mol%) and K_2CO_3 in *o*-xylene at 130 °C for 24 h. The Pd(II)-catalyzed arylation of **3b** with 1 or 2 equiv of **4a** yielded the tetraphenyl motif **6a** in 23-36% yield (Table 1) *via* the double (*ortho*) *β*-C-H arylation of biaryl carboxamide **3b**. The Pd(II)-catalyzed (*ortho*) *β*-C-H arylation of **3b** with 3 or 4 equiv of **4a** yielded the tetraphenyl motif **6a** in 72-80% yield. Additionally, the Pd(II)-catalyzed C-H arylation of **3b** with **4a** (4 equiv) using AgOAc instead of K_2CO_3 as an additive yielded **6a** in 60% yield (Table 1). All these trials involving the Pd(II)-catalyzed arylation of **3b** with **4a** yielded the tetraphenyl motif **6a** *via* the double (*ortho*) *β*-C-H arylation and we did not get the corresponding mono (*ortho*) *β*-C-H arylated product from substrate **3b**.

Next, we intended to expand the substrate scope and assemble a wide range of π-extended biaryls. Toward this, we attempted the preparation of terphenyls **5aa-5ar** using various carboxamides **7a,b, 3c-f, 8a-e, 9a, 10a**, and iodobiaryls **4b-d** (Scheme 3). The Pd(II)-catalyzed *β*-C-H arylation of heteroaryl carboxamides **7a,b** possessing the 8-aminoquionline DG with iodobiaryls **4b-d** afforded the corresponding terphenyl motifs **5aa-5ad** in 63-98% yields (Scheme 3). The Pd(II)-catalyzed *β*-C-H arylation of benzamides **3c-f** with iodobiaryls **4b,c** afforded the corresponding *p*-terphenyl motifs **5ae-5ai** in 46-73% yields. Then, we subjected the cinnamamide substrate **9a**[10a] to the *β*-C-H arylation with iodobiaryls **4b,c** in the presence of the $Pd(OAc)_2$ catalyst (10 mol%) and K_2CO_3 in *o*-xylene at 130 °C for 24 h. These reactions gave the corresponding acrylamide-based conjugated terphenyls **5aj,5ak** in 66-69% yields (Scheme 3).



[a] Substrate [0.38 mmol], ArI [4 equiv], $Pd[OAc]_2$ [10 mol%], AgOAc [2.5 equiv], toluene [3 mL], 110 °C, 48 h. [b] AgOAc [2.5 equiv] was used instead of K_2CO_3.

Scheme 3. Assembling of terphenyls *via* C-H arylation of carboxamides with iodobiaryls.

Subsequently, we attempted the preparation of terphenyls using arylacetamides *via* the *γ*-C(sp^2)-H (*ortho*) arylation.[8,10e] Accordingly, arylacetamides **8a-e** possessing the 8-aminoquionline DG were subjected to the Pd(II)-catalyzed *γ*-C-H (*ortho*) arylation with iodobiaryls **4b,c**. These reactions afforded the corresponding terphenyl motifs **5al-5aq** in 61-

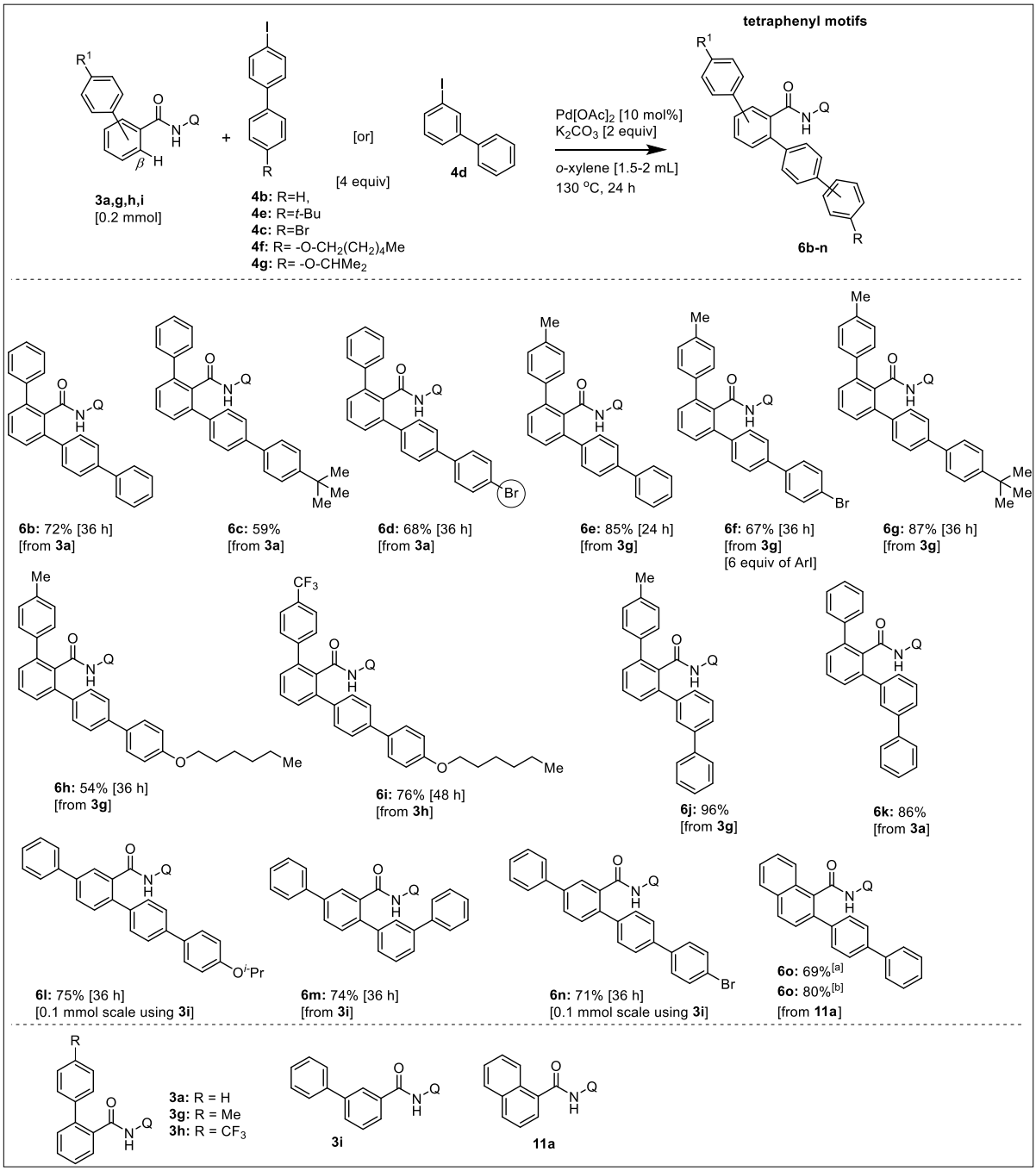
96% yields (Scheme 3). Similarly, we attempted the preparation of *para*-terphenyl using benzylamine derivative **10a** *via* the γ-C(sp^2)-H (*ortho*) arylation.[10g] Accordingly, the benzylamine derivative **10a** possessing the picolinamide DG was subjected to the Pd(II)-catalyzed γ-C(sp^2)-H (*ortho*) arylation with iodobiaryl **4b.** This reaction afforded the corresponding terphenyl motif **5ar** in 89% yield (Scheme 3).

We then focused our attention on the assembling of a wide range of tetraphenyls **6b-n** *via* the 8-aminoquinoline directing group-aided Pd(II)-catalyzed the β-C-H (*ortho*) arylation of biaryl carboxamides and iodobiaryls (Scheme 4). Towards this, we treated 2-biphenyl carboxamide **3a** with iodobiaryl **4b** or substituted 4-iodobiaryls **4c,e** in the presence of the $Pd(OAc)_2$ catalyst (10 mol%) and K_2CO_3 in *o*-xylene at 130 ^oC for 24-36 h. These reactions afforded the corresponding tetraphenyl motifs **6b-d** in 59-72% yields (Scheme 4). Similarly, 2-biphenyl carboxamide substrates **3g,h** were treated with 4-iodobiaryl **4b** or substituted 4-iodobiaryls **4c,e,f** were reacted in the presence of the $Pd(OAc)_2$ catalyst (10 mol%) and K_2CO_3 in *o*-xylene at 130 ^oC for 36-48 h. These reactions afforded the corresponding tetraphenyl motifs **6e-i** in 54-87% yields (Scheme 4).

Next, we performed the Pd(II)-catalyzed β-C-H (*ortho*) arylation of 2-biphenyl carboxamides **3a,g** with 3-iodobiphenyl **4d**. These reactions yielded the corresponding tetraphenyl motifs **6j,k** in 86-96% yields (Scheme 4). We then attempted the Pd(II)-catalyzed β-C-H (*ortho*) arylation using 3-biphenyl carboxamide substrate **3i** and 3-iodobiaryl **4d** or substituted 4-iodobiaryls **4c,g** in the presence of the $Pd(OAc)_2$ catalyst (10 mol%) and K_2CO_3 in *o*-xylene at 130 ^oC for 36 h. These reactions gave the corresponding tetraphenyl motif **6m** and tetraphenyls **6l,n** in 71-75% yields (Scheme 4). Furthermore, the Pd(II)-catalyzed 8-aminoquinoline-aided β-C-H (*ortho*) arylation of naphthalene-1-carboxamide **11a** and with 4-iodobiaryl **4b** yielded the corresponding tetraphenyl **6o** in 69-80% yields under two different conditions (Scheme 4).

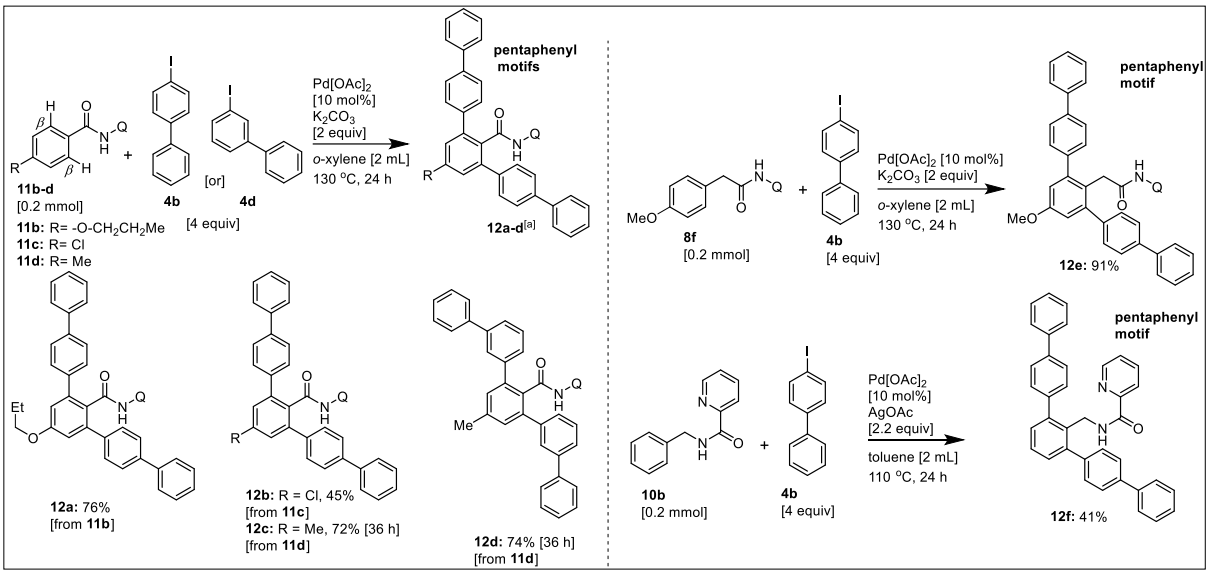
Having assembled the terphenyls, and tetraphenyls, we then wished to prepare pentaphenyl derivatives *via* the directing group-aided Pd(II)-catalyzed the β-C-H (*ortho*) arylation method. Towards this, we treated *para*-substituted carboxamide **11b** possessing the 8-AQ DG with iodobiaryl in the presence of the $Pd(OAc)_2$ catalyst (10 mol%) and K_2CO_3 in *o*-xylene at 130 ^oC for 24 h. This reaction afforded the expected pentaphenyl motif **12a** in 76% yield *via* the double β-C-H (*ortho*) arylation of benzamide **11b** (Scheme 5). Similarly, the Pd(II)-catalyzed double β-C-H (*ortho*) arylation of the *para*-substituted carboxamides **11c,d** possessing the 8-AQ DG with 4-iodobiaryl **4b** or 3-iodobiaryl **4d** afforded the corresponding pentaphenyl motifs **12b-d** in 45-74% yields (Scheme 5). The Pd(II)-catalyzed 8-aminoquinoline-aided double γ-C-H (*ortho*) arylation of arylacetamide derivative **8f** with 4-iodobiaryl **4b** yielded the

pentaphenyl motif **12e** in 91% yield (Scheme 5). Furthermore, the Pd(II)-catalyzed picolinamide-aided double *γ*-C-H (*ortho*) arylation of benzylamine derivatives **10b** with 4 -iodobiaryl **4b** yielded the pentaphenyl motif **12f** in 41% yield (Scheme 5).



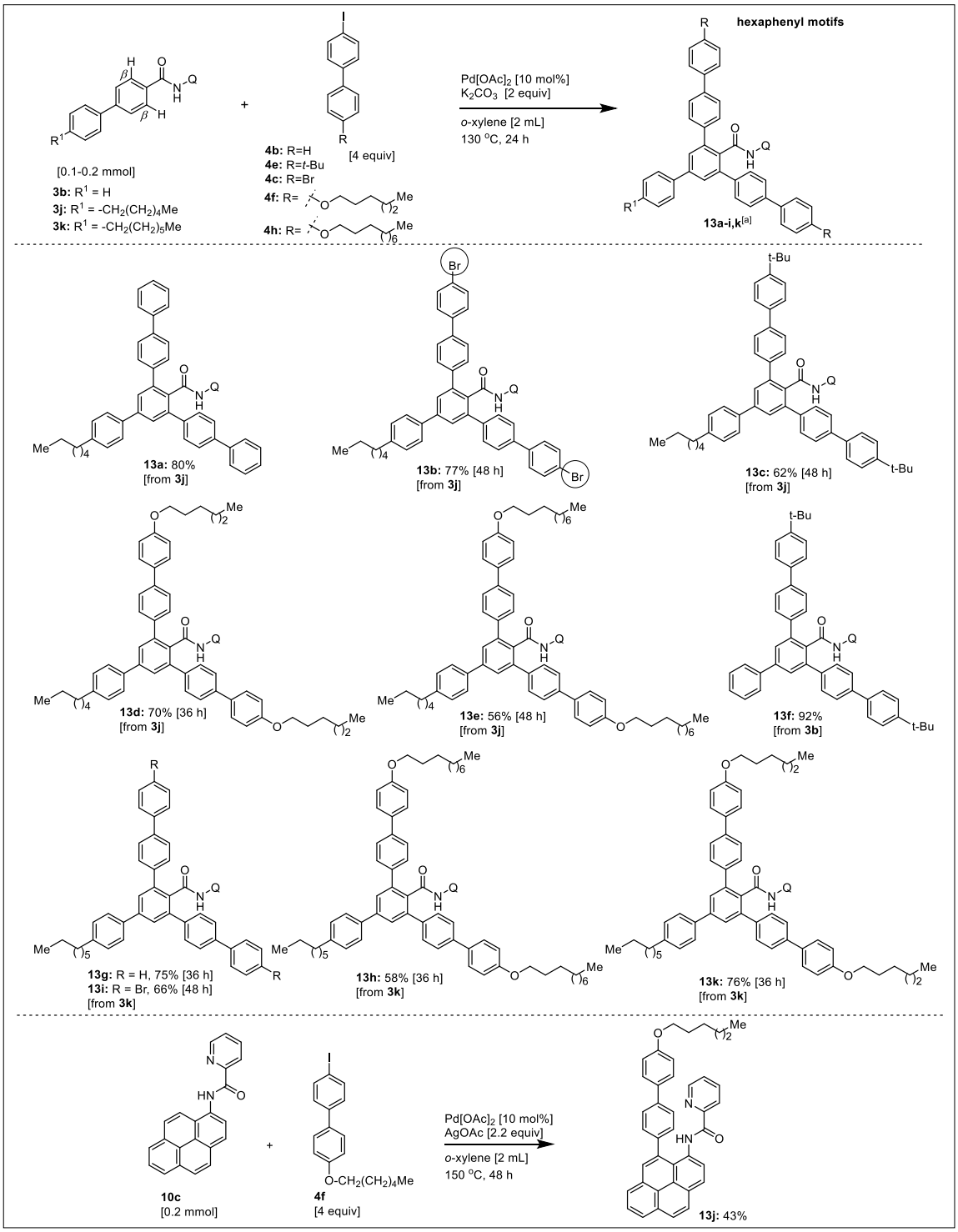
[a] $Pd[OAc]_2$ [10 mol%], AgOAc [2.2 equiv], toluene [2 mL], 110 °C, 36 h. [b] **11a** [0.1 mmol], $Pd[OAc]_2$ [10 mol%], K_2CO_3 [2 equiv], *o*-xylene [1.5 mL], 130 °C, 36 h.

Scheme 4. Assembling of tetraphenyls *via* C-H arylation of biaryl carboxamides.

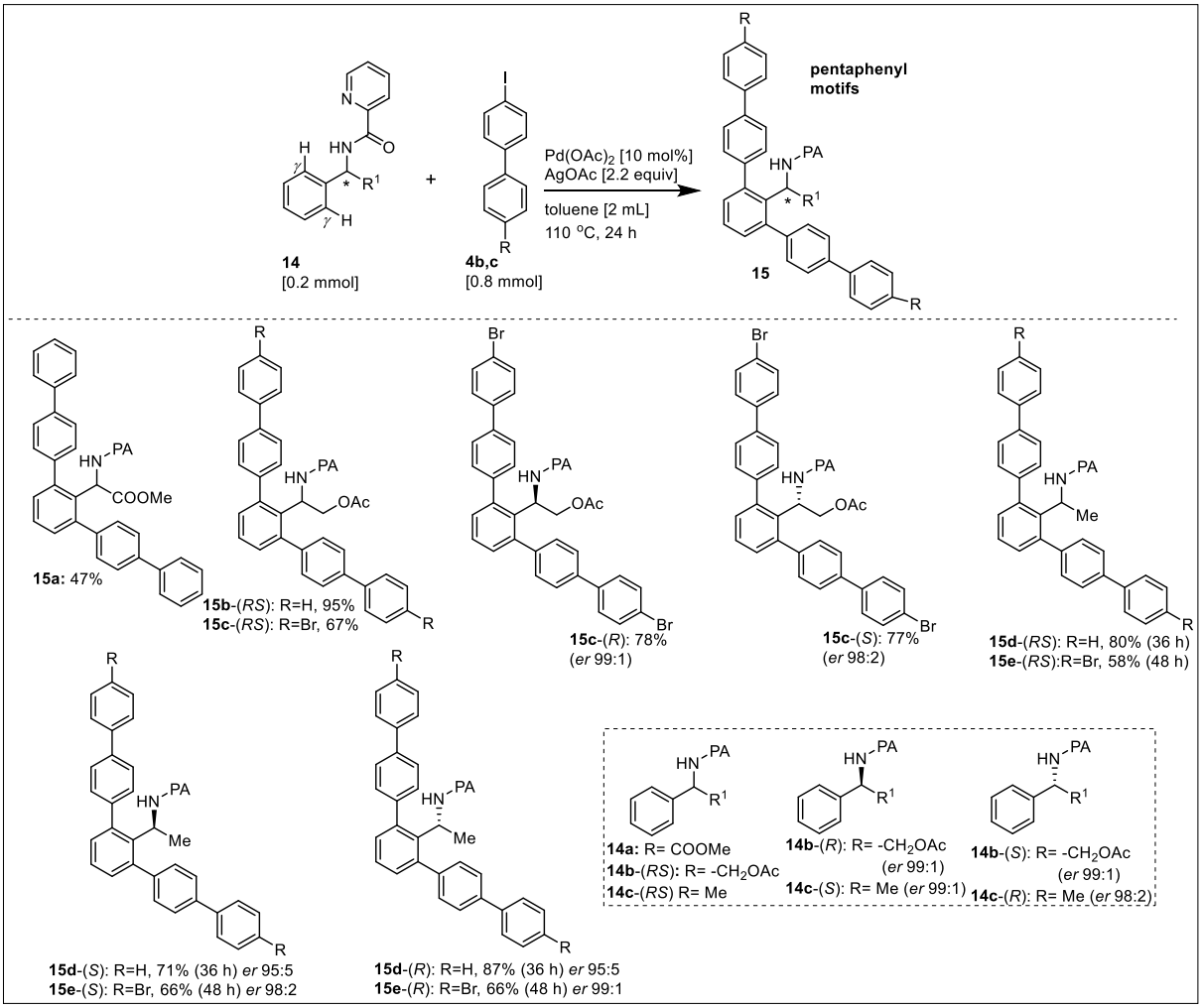


Scheme 5. Assembling of pentaphenyls.

We then continued with our efforts to assemble hexaphenyl derivatives **13a-i,k** *via* the Pd(II)-catalyzed double *β*-C-H (*ortho*) arylation method (Scheme 6). Accordingly, we subjected 4-biphenyl carboxamide **3j** possessing the 8-AQ DG to the double *β*-C-H (*ortho*) arylation using 4-iodobiaryl **4b** in the presence of the $Pd(OAc)_2$ catalyst (10 mol%) and K_2CO_3 in *o*-xylene at 130 ^oC for 24 h. This reaction gave the expected and interesting hexaphenyl motif **13a** in 80% yield in a single transformation (Scheme 6). Then, 4-biphenyl carboxamides **3j** was subjected to the Pd(II)-catalyzed double *β*-C-H (*ortho*) arylation using various 4-iodobiaryls **4c,e,f,h** and these reactions yielded the corresponding hexaphenyl motifs **13b-e** in 56-77% yields (Scheme 6). To further expand the substrate scope, we treated 4-biphenyl carboxamides **3b,k** with 4-iodobiaryls **4b,c,e,f,h** in the presence of the $Pd(OAc)_2$ catalyst (10 mol%) and K_2CO_3 in *o*-xylene at 130 ^oC for 24-48 h. These reactions yielded the corresponding hexaphenyl motifs **13f,g,h,I,k** in 58-92% yields *via* the double *β*-C-H (*ortho*) arylation of 4-biphenyl carboxamides **3b,k** (Scheme 6). Furthermore, the Pd(II)-catalyzed picolinamide-aided *γ*-C(sp^2)-H arylation of pyrene derivative **10c**[10f] with 4-iodobiaryl **4f** yielded the hexaphenyl motif **13j** in 43% yield (Scheme 6).



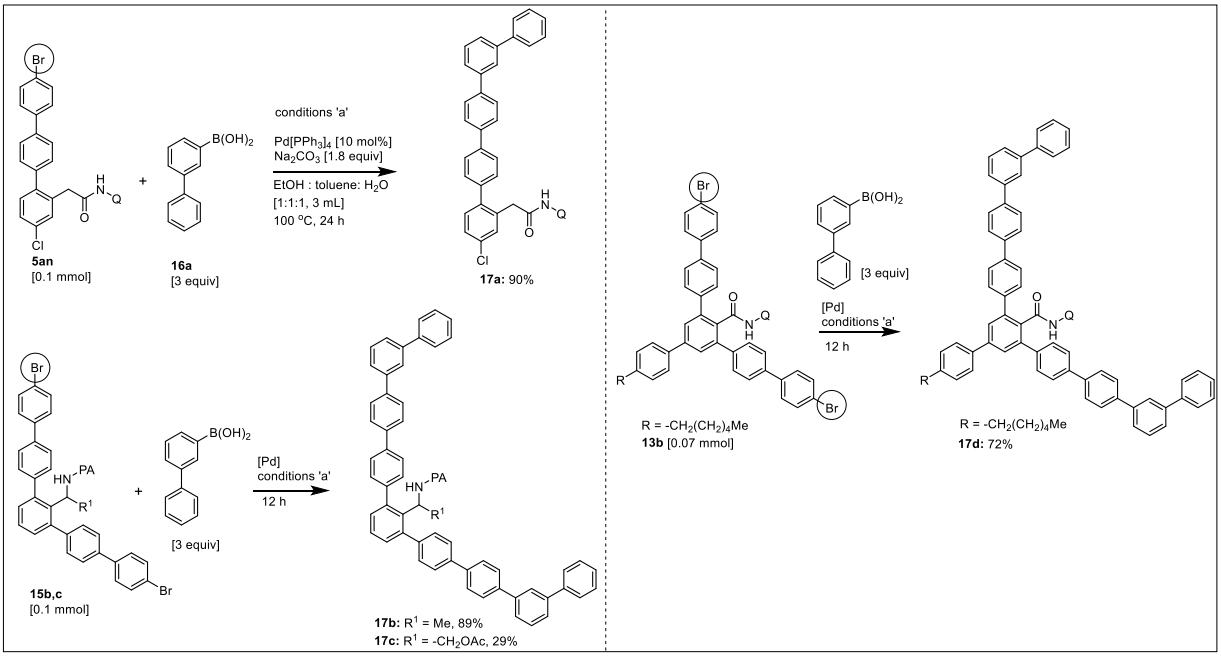
Scheme 6. Assembling of hexaphenyls.



Scheme 7. Assembling of pentaphenyls based on racemic and enantiopure phenylalaninol and *α*-methyl benzylamine.

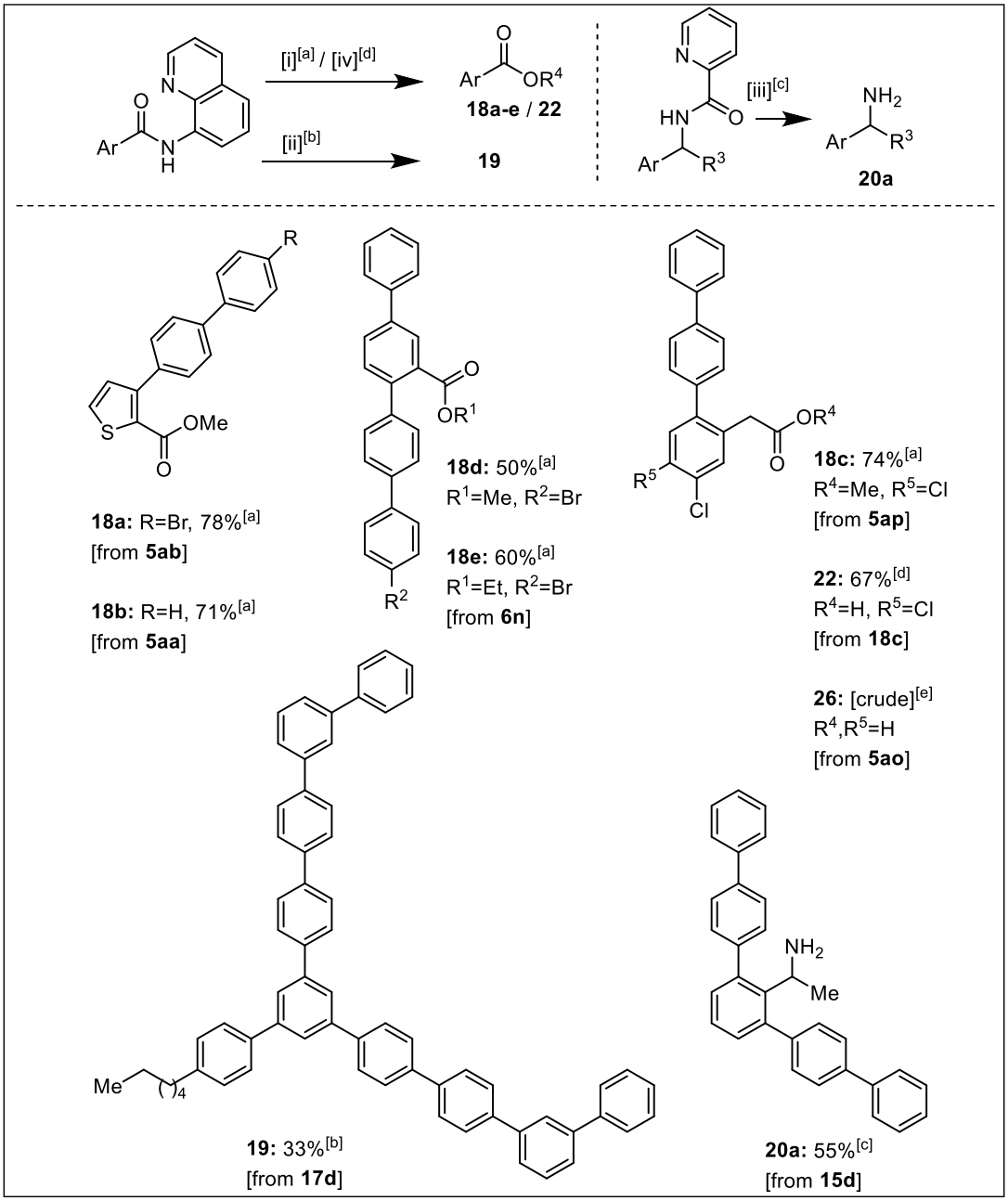
Next, we wished to prepare the enantiopure polyaryl (π-extended polyaryl) compounds through the picolinamide directing group-aided Pd(II)-catalyzed C-H arylation method.[10g] Towards this, we attempted the Pd(II)-catalyzed picolinamide-aided double *γ*-C-H (*ortho*) arylation of racemic phenylglycinol **14a**-(*RS*) with iodobiaryls **4b,c** and these reactions gave the corresponding pentaphenyl-based amino alcohol derivatives **15a** and **15c** in 66-95% yields (Scheme 7). Subsequently, the enantiopure phenylglycinols **14a**-(*R*) and **14a**-(*S*) were subjected to the Pd(II)-catalyzed picolinamide-aided double *γ*-C-H (*ortho*) arylation with **4c**. These reactions gave the corresponding enantiopure pentaphenyl-based amino alcohol derivatives **15c**-(*R*) (78% yield, *er* 99:1) and **15c**-(*S*) (77% yield, *er* 99:1). To further expand the substrate scope, we attempted the Pd(II)-catalyzed picolinamide-aided double *γ*-C-H (*ortho*) arylation of racemic *α*-methyl benzylamine derivative **14b** with **4b,c** and these reactions gave the corresponding pentaphenyl motifs **15b** and **15d** in 58-80% yields. Next, the enantiopure *α*-methyl benzylamine derivatives **14b**-(*R*) and **14b**-(*S*) were subjected to the Pd(II)- catalyzed picolinamide-aided double *γ*-C-H (*ortho*) arylation with **4b,c**. These reactions

gave the corresponding enantiopure pentaphenyl-based *α*-methylbenzylamine derivatives **15b**-(*R*) (66% yield, *er* 99:1), **15b**-(*S*) (66% yield, *er* 99:1), **15d**-(*R*) (87% yield, *er* 95:5), **15d**-(*S*) (71% yield, *er* 95:5) (Scheme 7).



Scheme 8. Representative examples of the extension of the aryl ring *via* cross-coupling reaction and synthesis of polyaryls.

Then, we intended to increase the synthetic utility of this protocol comprising the assembling of π-extended polyaryls through the Pd(II)-catalyzed C-H arylation method by taking the help of the cross-coupling method.[1] Towards this initially, we attempted the Suzuki-Miyaura coupling reaction of pentaphenyl derivative **5an** having a bromo substituent at the terminal phenyl moiety. Accordingly, the Pd-catalyzed Suzuki coupling of **5an** with 3-biphenylboronic acid **16a** yielded the pentaphenyl motif **17a** in 90% yield (Scheme 8). We then attempted the Suzuki coupling reaction of pentaphenyl derivatives **15b,c** having two bromo substituents at the terminal phenyl moieties. Accordingly, the Pd- catalyzed Suzuki coupling of **15b,c** with 3-biphenylboronic acid **16a** yielded the corresponding polyaryl motifs **17b,c** in 29-89% yields. Additionally, we attempted the Pd-catalyzed Suzuki coupling of **13b** with 3-biphenylboronic acid **16a**, which yielded the corresponding polyaryl motif **17d** in 72% yield (Scheme 8).

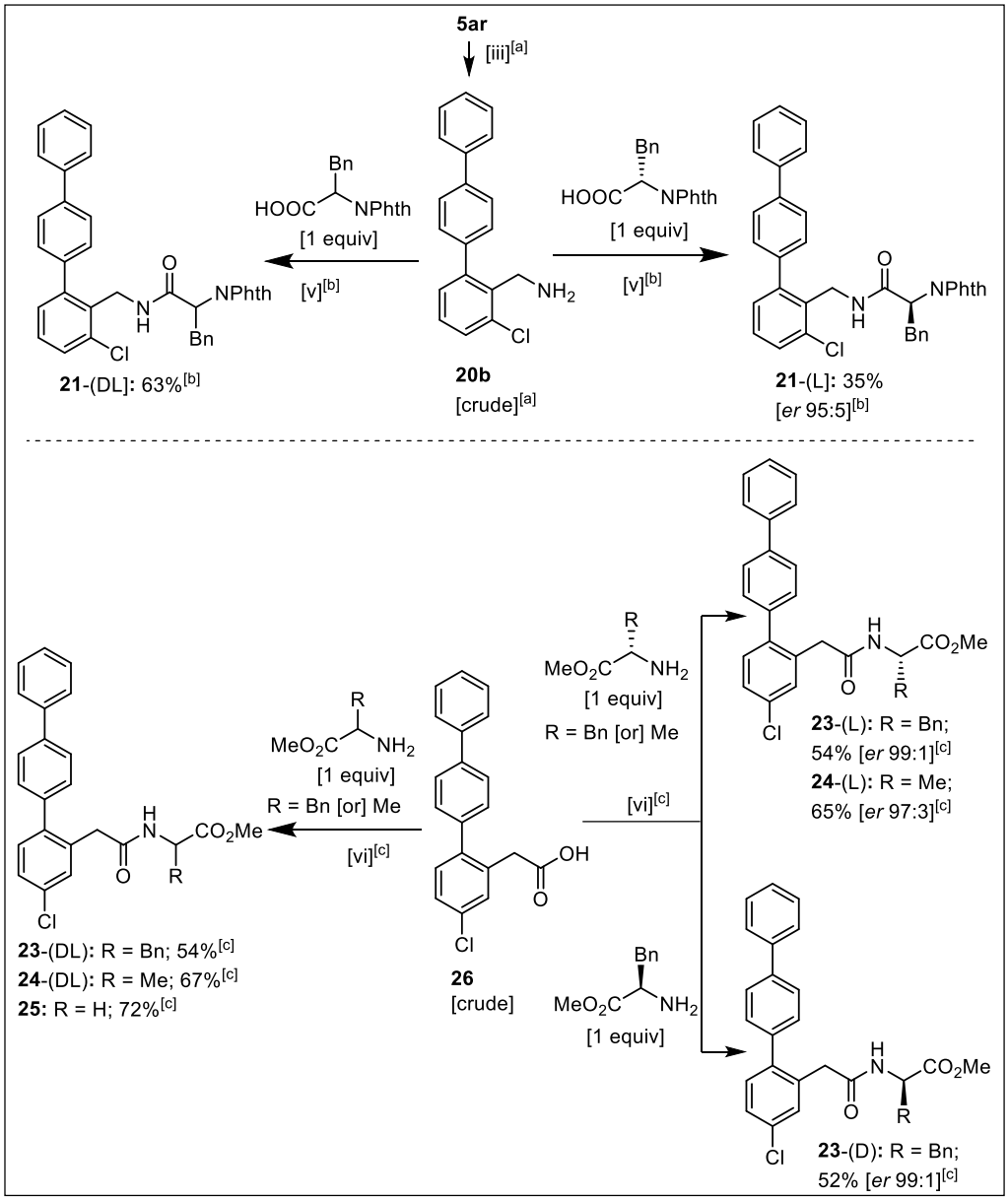


[a] Obtained using corresponding substrate [0.2-0.5 mmol], $BF_3{\cdot}OEt_2$ [10-15 equiv], MeOH [or] EtOH [2-3 mL] 90-140 °C, 24-36 h. [b] Obtained using corresponding substrate [0.04 mmol], TfOH [0.08 mL], toluene:H_2O [0.8:0.08 mL], 100 °C, 24 h. [c] Obtained using corresponding substrate [0.09 mmol], Zn dust [15 equiv], HCl [12 N, 0.25 mL], THF:H_2O [1:1 mL], rt, 24 h. open flask.[d] LiOH [1M aq. solution in H_2O, 24 mg in 1 mL H_2O], MeOH [2 mL], rt, 24 h [e] Obtained using corresponding substrate [1 equiv], NaOH [40 equiv], EtOH [2 mL], 100 °C, 48 h, sealed tube.

Scheme 9. Synthetic utility of synthesized π-extended biaryls.

Furthermore, we performed the removal of the directing groups from the synthesized π-extended biaryl compounds. Treatment of terphenyl carboxamides **5aa,5ab,5ap**, and tetraphenyl carboxamides **6n** with $BF_3{\cdot}OEt_2$ in MeOH or EtOH afforded the corresponding ester compounds **18a-e** *via* the direct conversion amide into ester method (Scheme 9). The LiOH-mediated hydrolysis of terphenyl ester **18c** afforded the corresponding terphenyl

carboxylic acid **22**. Notably, treatment of **17d** with TfOH directly gave the decarboxylated polyaryl derivative **19** (Scheme 9). Treatment of picolinamide derivative **15d** with Zn dust/HCl in THF:H_2O gave the corresponding benzylamine derivative **20a**. Along this line, the treatment of picolinamide derivative **5ar** with Zn dust/HCl, in THF:H_2O gave the corresponding benzylamine derivative **20b (**Scheme 10). Subsequently, **20b** was treated with *N*-phthaloyl phenylalanines ((DL) or (L)) to afford the corresponding amide derivatives **21**-(DL) (63% yield) and enantiopure **21**-(L) (35% yield, *er* 95:5).



[a] Obtained using corresponding substrate [0.09-0.15 mmol], Zn dust [15 equiv], HCl [12 N, 0.25 mL], THF:H_2O [1:1 mL], rt, 24 h. [b] EDC-HCl [1.1 equiv], HOBt [1.1 equiv], DCM [20 mL], 0 °C to rt, 24 h. [c] Obtained using corresponding substrate [0.075-0.1 mmol], EDC·HCl [1.1 equiv], HOBt [1.1 equiv], DCM [20 mL], 0 °C to rt, 1 h and then, amino acid ester hydrochloride, rt, 24 h.

Scheme 10. Synthetic utility of synthesized π-extended biaryls.

Along this line, terphenyl carboxylic acid **26** (which was obtained from **5ao**) was treated with glycine hydrochloride or phenylalanines ((DL) or (L) or (D)) or alanines ((DL) or (L)) to afford the corresponding terphenyl-based amide derivatives. Accordingly, the amide derivatives **25** (72% yield), **23**-(DL) (54% yield), **24**-(DL) (67% yield), and enantiopure **23**-(L) (54% yield, *er* 99:1), **23**-(D) (52% yield, *er* 99:1) and **24**-(L) (65% yield, *er* 97:3) were synthesized in moderate to good yields (Scheme 10).

In general, the mechanism of the bidentate directing group 8-aminoquinoline-directed C–H activation and arylation of (*ortho*) *β*-C-H bond of benzamide-type systems is well documented.[8-10,15] Similarly, the mechanism of the bidentate directing group picolinamide-directed C–H activation and arylation of (*ortho*) *γ*-C-H bond of benzylamine-type systems is well documented. Accordingly, in concurrence with literature reports, the bidentate directing group-directed *ortho* C(sp^2)-H functionalization reaction of substrates investigated in this paper is believed to undergo *via* the well-documented Pd^{II}-Pd^{IV} catalytic cycle.[8-10,15] Along this line, plausible reaction pathways for the Pd(II)-catalyzed 8-aminoquinoline directing group-aided

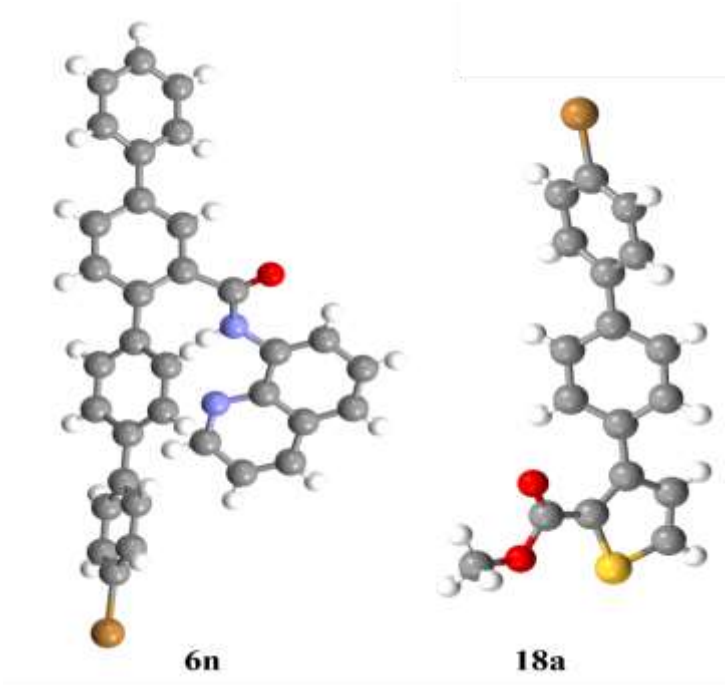
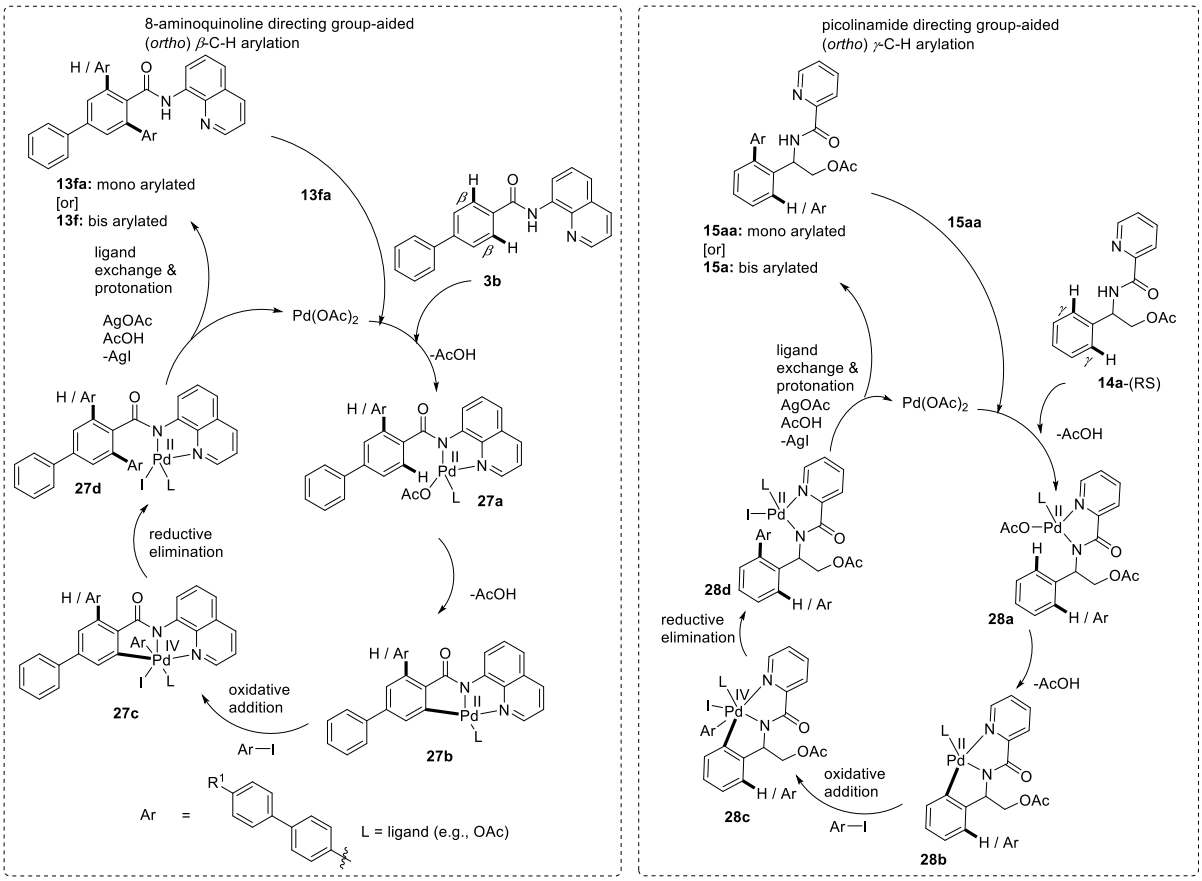


Figure 2. X-ray structures (ball and stick models) of the π-extended biaryl (polyaryl) compounds **6n** and **18a**.

β-C-H arylation and picolinamide directing group-aided *γ*-C-H arylation of the corresponding carboxamides are proposed (Scheme 11). The coordination of the 8-aminoquinoline directing group in biaryl carboxamide **3b** to the Pd(II) metal center results in the species **27a** and is followed by concerted metalation deprotonation (CMD), generating the five-membered Pd(II) intermediate **27b**. Oxidative addition of the Pd(II) species **27b** with biaryl iodide then forms

the Pd(IV) intermediate **27c**. Then the Pd(IV) intermediate undergoes reductive elimination to generate the new C–C bond in the intermediate **27d**. Halide group abstraction by a halide ion scavenger (e.g., AgOAc) followed by the protonolysis of the intermediate **27d** generates the mono *β*-C-H arylated product **13fa** and the active Pd(II) species is regenerated in the catalytic cycle (Scheme 11). Then, the mono *β*-C-H arylated product **13fa** will undergo the second *β*-C-H arylation under the sequences described above to afford the bis *β*-C-H arylated product **13f**. Similarly, the Pd(II)-catalyzed picolinamide directing group-aided mono (*ortho*) *γ*-C-H arylation of **14a**-(*RS*) is proposed to afford **15aa** *via* the intermediates **28a-d**. Then, the mono *γ*-C-H arylated product **15aa** will undergo the second *γ*-C-H arylation under the sequences described to afford the bis *γ*-C-H arylated product **15a** (Scheme 11). It is a general trend that the C-H arylation of aromatic substrates containing two equivalent *ortho β*-C-H or *γ*-C-H bonds afforded the bis C-H arylated products.[8-10] The mono C-H arylated products from the C-H arylation of aromatic substrates containing two equivalent *ortho β*-C-H or *γ*-C-H bonds are seldom obtained.[8-10] For example, under suitably optimized conditions or using a moderately efficient directing group the mono C-H arylation product can be obtained.[10i] In the current investigation, the C-H arylation of aromatic substrates containing two equivalent *ortho β*-C-H or *γ*-C-H bonds afforded the bis C-H arylated products as the major products. Furthermore, in the reactions discussed in this work, the C-H arylated products were obtained in satisfactory to good yields. We did not obtain any side or by-products in demonstrable amounts.

We then ascertained the UV-Vis absorption data λ_{max} (nm) of all the compounds prepared in this work[16] (the corresponding UV-Vis absorption spectra have been given in the supplementary information). The synthesized polyaryl (π-extended biaryl) compounds were characterized by NMR and HRMS analysis data. Additionally, the X-ray structure of compounds **6n** and **18a** were obtained (Figure 2),[17] which corroborated the Pd(II)-catalyzed bidentate directing group-aided selective (*ortho*) *β*-C-H arylation of the corresponding carboxamides with iodobiaryls as the coupling partners.



Scheme 11. Proposed mechanism in concurrence with the literature. [8-10,15] Pd(II)-catalyzed 8-aminoquinoline directing group-aided *β*-C-H arylation and picolinamide directing group-aided *γ*-C-H arylation of the corresponding carboxamides.

Conclusion

In summary, we have shown our efforts of extending the chemistry of Pd(II)-catalyzed bidentate directing group-aided (*ortho*) *β*- or *γ*-C-H arylation method for constructing the polyaryl (π-extended biaryl) compounds using biaryl-based carboxamides and iodobiaryls as the coupling partners. We have shown the usefulness of both the 8-aminoquinoline- and picolinamide-assisted (*ortho*) *β*- or *γ*-C-H arylation methods for constructing polyaryl (polyphenylene) compounds. A wide range of polyaryl compounds (π-extended biaryl or polyphenylenes) were assembled, including terphenyls, tetraphenyls, pentaphenyls, and hexaphenyls. Additionally, we have performed the Suzuki-Miyaura coupling on representative compounds containing a bromide substituent which were assembled *via* C-H arylation. This process has helped in extending the aryl rings in substrates to afford π-extended polyaryls (polyphenylenes). Additionally, we have assembled examples of enantiopure terphenyl and penta-aryl derivatives. Traditionally, catalytic aryl-aryl cross-coupling protocols involving organometallic reagents such as aryl boronic acids and aryl magnesium reagents were employed to assemble π-extended biaryls and polyaryl molecules. In general, the availability

or pre-assembling of organometallic reagents limits the elaboration of the substrate scope development in investigations pertaining to aryl-aryl cross-couplings affording polyaryls. In the current work, in a single operation of C-H coupling of biaryl-based carboxamides and iodobiaryls, various π-extended biaryl and polyaryl molecules have been assembled. The π-extended poly aromatic compounds (e.g., teraryls, quateraryls, penta-aryls) have gained importance as biologically active compounds, precursors of molecular devices, and functional materials. Accordingly, it is believed that the current investigation on the bidentate DG-aided C-H arylation of biaryl-based carboxamides with iodobiaryls would serve as an alternative and quick route to enrich the library of the π-extended polyaromatic compound building blocks.

Experimental Section

General. ^{1}H and $^{13}C\{^{1}H\}$ NMR spectra of compounds were recorded (using TMS as an internal standard) in 400 and ~101 MHz spectrometers, respectively. The HRMS analysis data of samples were obtained from QTOF mass analyzer using the electrospray ionization (ESI) method. FT-IR spectra of compounds were recorded as neat or thin films. Column chromatography purification was carried out on silica gel (100−200 mesh). Reactions were conducted in anhydrous solvents under a nitrogen atm wherever required. Organic layers obtained after the workup were dried using anhydrous Na_2SO_4. Thin layer chromatography (TLC) analyses were performed on silica gel or alumina plates and components were visualized by UV light or using iodine vapor. Isolated yields of all the products are reported and yields were not optimized. The required 8-aminoquinoline-linked carboxamides or picolinamide-linked carboxamides were synthesized under the standard amide coupling method. [8-10] Most of the carboxamide starting materials used in this work are known compounds in the literature or used by us earlier and were prepared using standard methods. [8-10]

Procedure for the synthesis of the 8-aminoquinoline directing group linked carboxamides (procedure A): A dry RB flask containing amine (1.0 equiv), Et_3N (1.2 equiv) was stirred for 5-10 min under a nitrogen atm. Then, to the reaction flask was added anhydrous DCM (4 mL) followed by dropwise addition of the corresponding acid chloride, which was prepared from the corresponding carboxylic acid (1.0 equiv), DMF (cat.) and $(COCl)_2$ (1.2 equiv) in 0 ^{o}C for 3-4 h. Then, the reaction mixture was stirred overnight. After this period, the reaction mixture was diluted with dichloromethane (10-15 mL) and washed with water (10-15 mL) and twice with saturated aqueous $NaHCO_3$ solution (10-15 mL). The combined organic layers were washed with HCl (1 N) (10 mL x 2) to remove excess amine and then dried over anhydrous

Na_2SO_4, concentrated in a vacuum to afford the corresponding crude carboxamides which were purified by column chromatography.

General procedure for the Pd(II)-catalyzed C-H arylation of the carboxamides using iodobiaryls (procedure B): An appropriate carboxamide (0.2 mmol, 1 equiv), an appropriate aryl iodide (0.8 mmol, 4 equiv), $Pd(OAc)_2$ (4.5 mg, 10 mol%) and K_2CO_3 (0.4 mmol, 2.0 equiv) in *o*-xylene (2 mL) was heated at 130 ^oC for 24-48 h under a nitrogen atm. After the reaction period, the reaction mixture was concentrated in a vacuum and purification of the resulting reaction mixture by column chromatography on neutral alumina or silica gel (eluent = EtOAc:hexanes) furnished the corresponding arylated carboxamide (see the corresponding Tables/Schemes for specific examples).

Procedure for the synthesis of compound 17a-d (procedure C): A mixture of corresponding arylated carboxamides (0.1 mmol), 3-biphenylboronic acid (3.0 equiv), Na_2CO_3 (2 equiv), $[Pd(PPh_3)_4]$ (5 mol%) and tolune:EtOH:H_2O (1:1:1) (3 mL) were added to a screw-cap sealed tube. Nitrogen was purged before the tube was submerged into a silicon oil bath preheated to 100 ^oC and the reaction was continued for 12 h. After cooling to rt, the product was extracted with ethyl acetate. The organic layers were collected, and dried over anhydrous Na_2SO_4, and the solvent was evaporated. The crude mixture was subjected to column chromatography to afford the compound **17a-d** (**17a** was synthesized using 3-biphenylboronic acid (1.5 equiv)).

Procedure for the synthesis of compound 20a (Procedure D): To a RB flask containing an appropriate picolinamide of *α*-methyl benzylamine derivatives (0.09 mmol) dissolved in H_2O/THF (1:1, 2 mL), 12 N HCl (0.25 mL) was added. The mixture was stirred at rt for 15 min. Zinc dust (15 equiv) was then added in three portions and the mixture was stirred at rt for 12-24 h. The reaction mixture was transferred to a separating funnel with 2 M NaOH (25 mL) and extracted with ethyl acetate. The organic layers were collected, and dried over anhydrous Na_2SO_4 and the solvent was evaporated. The crude mixture was subjected to column chromatography to afford the compound **20a**.

Procedure for the synthesis of compound 19 (Procedure E): A mixture of carboxamide **17d** (0.04 mmol), TfOH (0.08 mL), and toluene:H_2O (1:0.1, v/v) (0.88 mL) were suspended in a 10 ml capacity sealed (pressure) tube, sealed with a PTFE-lined cap, stirred at 100 ^oC for 24 h. After the completion of the reaction period, the reaction mixture was diluted with EtOAc (10 mL) and washed with Na_2CO_3 (5 mL x 2). The organic layers were collected, dried over

anhydrous Na_2SO_4, and concentrated in a vacuum. The crude mixture was then purified using column chromatography on silica gel (EtOAc:hexane) to furnish the corresponding product **19**.

Procedure for the synthesis of compound 18a-e (Procedure F): A mixture of an appropriate carboxamide (0.21–0.41 mmol,1 equiv), BF_3–Et_2O (15 equiv) and corresponding anhydrous methanol or ethanol (2-3 mL) in a crew-capped sealed tube containing a magnetic bead purged with N_2 was stirred and heated at 90-140 ^oC for 24-36 h. Then, the reaction mixture was allowed to attain the rt and concentrated under reduced pressure to afford the corresponding crude reaction mixture, which was purified by column chromatography to afford corresponding ester derivatives **18a-e**.

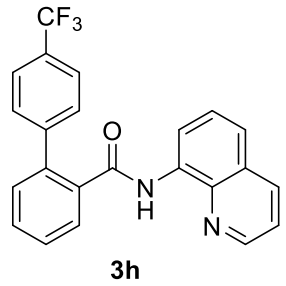
Procedure for the hydrolysis of ester derivative (Procedure G1): An appropriate ester derivative (1 equiv) was dissolved in MeOH (2 mL) in an RB flask. To this LiOH (1M aq. solution in H_2O, 24 mg in 1 mL H_2O) was added and the reaction mixture was stirred for 24 h in the open air. After the reaction was over, the reaction mixture was quenched with 1 N HCl solution. The aq. layer was extracted with DCM (3 times) and dried over anhydrous sodium sulphate, concentrated in a vacuum, and further purified using column chromatography.

Procedure for the hydrolysis of amide derivative (Procedure G2): Arylated carboxamide (1 equiv) and NaOH (40 equiv) in ethanol (2 mL) were heated at 100 °C for 48 h in a sealed tube (flushed with ambient air). After this period, the reaction mixture was diluted with water and extracted with ethyl acetate (2 × 10 mL), and then the water part was acidified with 1 N HCl to get a pH ≈ 2. Extraction with ethyl acetate (2 × 10 mL) and drying of the combined organic layers over Na_2SO_4 followed by evaporation of the solvent in a vacuum afforded the corresponding carboxylic acid which was used for the next step without purification.

Procedure for the synthesis of compound 21-(DL), **21**-(L) **(Procedure H):** An appropriate amount of *N*-protected phenylalanine (1 equiv), *N*-(3-dimethylaminopropyl)-*N*′-ethylcarbodiimide hydrochloride (1.1 equiv), 1-hydroxybenzotriazole hydrate (1.1 equiv) in DCM (20 mL) was stirred for 1 h at 0 °C under a nitrogen atmosphere. Then, an appropriate amount of **20b** (1 equiv) was added to the above mixture and stirred for 24 h at room temperature. The resulting solution was then subjected to aqueous workup and washed with aqueous $NaHCO_3$ solution (two times). The resulting solution mixture was concentrated and purified on silica gel column chromatography (EtOAc/hexane) to give the corresponding **21**-(DL), **21**-(L).

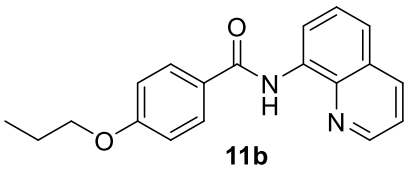
Procedure for the synthesis of compound 23-(DL), **23**-(L), **23**-(D), **24**-(DL), **24**-(L), **25 (Procedure I):** An appropriate amount of corresponding acid (1 equiv), *N*-(3-dimethylaminopropyl)-*N′*-ethylcarbodiimide hydrochloride (1.1 equiv), 1-hydroxybenzotriazole hydrate (1.1 equiv) in DCM (20 mL) was stirred for 1 h at 0 °C under a nitrogen atm. Then, an appropriate amount of corresponding C-protected amino acid (1 equiv) was added to the above mixture and stirred for 24 h at room temperature. The resulting solution was then subjected to aqueous workup and washed with aqueous $NaHCO_3$ solution (two times). The resulting solution mixture was concentrated and purified on silica gel column chromatography (EtOAc/hexane) to give the corresponding **23**-(DL), **23-(**L**), 23**-(D), **24**-(DL), **24**-(L) and **25**.

***N*-(Quinolin-8-yl)-4'-(trifluoromethyl)-[1,1'-biphenyl]-2-carboxamide (3h):** Following the general procedure A, **3h** was obtained after purification by column chromatography on silica gel (EtOAc:Hexane = 20:80) as brown solid (501 mg, 64%, 2 mmol scale); R_f = 0.4 (EtOAc:Hexane = 20:80); mp: 147-149 °C; IR (DCM): 3319, 1673, 1528, 1326, 1127 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ_H 9.82 (1H, s), 8.80 (1H, dd, J_1 = 7.2 Hz, J_2 = 1.4 Hz), 8.53 (1H, dd, J_1 = 4.2 Hz, J_2 = 1.5 Hz), 8.12 (1H, dd, J_1 = 8.3 Hz, J_2 = 1.5 Hz), 7.987 (1H, dd, J_1 = 7.4 Hz, J_2 = 1.2 Hz), 7.66–7.63 (2H, m), 7.62–7.60 (1H, m), 7.59–7.50 (6H, m), 7.39 (1H, dd, J_1 = 8.3 Hz, J_2 = 4.2 Hz), $^{13}C\{^1H\}$ NMR (~101 MHz, $CDCl_3$): δ_C 167.2, 147.9, 143.8, 138.9, 138.3, 136.2, 136.1, 134.3, 130.8, 130.6, 129.7 (q, $J_{C\text{-}F}$ = 128.4 Hz), 129.4, 128.5, 127.8, 127.2, 125.5, 125.3 (q, $J_{C\text{-}F}$ = 3.5 Hz), 124.1 (q, $J_{C\text{-}F}$ = 270.0 Hz), 121.9, 121.5, 116.4. HRMS (ESI): *m/z* $[M+H]^+$ calcd for $C_{23}H_{16}F_3N_2O$: 393.1215 found, 393.1226.



3h

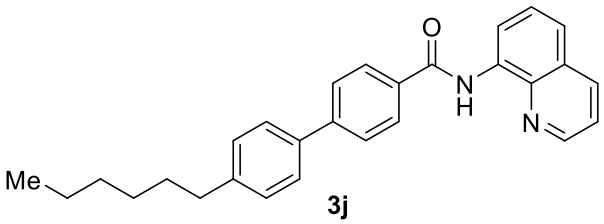
4-Propoxy-*N*-(quinolin-8-yl)benzamide (11b): Following the general procedure A, **11b** was obtained after purification by column chromatography on silica gel (EtOAc:Hexane = 20:80) as colourless solid (470 mg, 77%, 2 mmol scale); R_f = 0.5 (EtOAc:Hexane = 20:80); mp: 99-101 °C; IR (DCM): 3364, 2946, 1665, 1503, 1247 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ_H 10.71 (1H, s), 8.95 (1H, dd, J_1 = 7.6 Hz, J_2 = 1.3 Hz), 8.88 (1H, dd, J_1 = 4.2 Hz, J_2 = 1.7 Hz), 8.21 (1H, dd, J_1 = 8.2 Hz, J_2 = 1.6 Hz), 8.07 (2H, dt, J_1 = 8.8 Hz, J_2 = 2.0 Hz), 7.64–7.60 (1H, m), 7.55 (1H, dd, J_1 = 8.2 Hz, J_2 = 1.3 Hz), 7.50 (1H, dd, J_1 = 8.2 Hz, J_2 = 4.2 Hz), 7.05 (2H, dt, J_1 = 8.8 Hz, J_2 = 2.0 Hz), 4.04 (2H, t, J = 6.6 Hz), 1.91–1.86 (2H, m), 1.10 (3H, t, J = 7.4 Hz); $^{13}C\{^1H\}$ NMR (~101 MHz, $CDCl_3$): δ_C 165.1,



11b

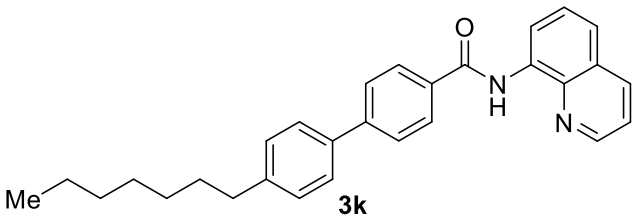
162.1, 148.2, 138.8, 136.4, 134.8, 129.2, 128.0, 127.6, 127.2, 121.7, 121.4, 116.4, 114.5, 69.7, 22.5, 10.5; HRMS (ESI): *m/z* $[M+H]^+$ calcd for $C_{19}H_{19}N_2O_2$: 307.1447 found, 307.1434.

4'-Hexyl-*N*-(quinolin-8-yl)-[1,1'-biphenyl]-4-carboxamide (3j): Following the general procedure A, **3j** was obtained after purification by column chromatography on silica gel (EtOAc:Hexane = 20:80) as brown solid (538 mg, 44%, 3 mmol scale); R_f = 0.6 (EtOAc:Hexane = 20:80); mp: 95-97 °C; IR (DCM): 3242, 1609, 1534, 1483, 1267 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ_H 10.83 (1H, s), 8.99 (1H, dd, J_1 = 7.5 Hz, J_2 = 1.3 Hz), 8.90 (1H, dd, J_1 = 4.2 Hz, J_2 = 1.6 Hz), 8.23 (1H, dd, J_1 = 8.3 Hz, J_2 = 1.6 Hz), 8.18 (2H, dt, J_1 = 8.4 Hz, J_2 = 1.7 Hz), 7.79 (2H, dt, J_1 = 8.4 Hz, J_2 = 1.6 Hz), 7.66–7.57 (4H, m), 7.52 (1H, dd, J_1 = 8.2 Hz, J_2 = 4.2 Hz), 7.33 (2H, d, J = 8.1 Hz), 2.70 (2H, t, J = 7.8 Hz), 1.71–1.65 (2H, m), 1.42–1.33 (6H, m), 0.94–0.91 (3H, m). $^{13}C\{^1H\}$ NMR (~101 MHz, $CDCl_3$): δ_C 165.2, 148.3, 144.6, 143.1, 138.8, 137.2, 136.4, 134.6, 133.4, 129.0, 128.0, 127.8, 127.5, 127.2, 127.1, 121.7, 116.5, 35.7, 31.7, 31.4, 29.0, 22.6, 14.1. HRMS (ESI): *m/z* $[M+H]^+$ calcd for $C_{28}H_{29}N_2O$: 409.2280 found, 409.2290.



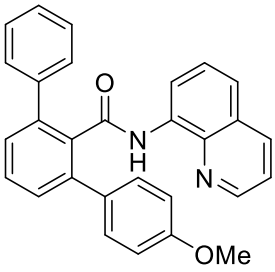
3j

4'-Heptyl-*N*-(quinolin-8-yl)-[1,1'-biphenyl]-4-carboxamide (3k): Following the general procedure A, **3k** was obtained after purification by column chromatography on silica gel (EtOAc:Hexane = 20:80) as brown solid (540 mg, 34%, 3 mmol scale); R_f = 0.6 (EtOAc:Hexane = 20:80); mp: 90-92 °C; IR (DCM): 3357, 1610, 1534, 1483, 1266 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ_H 10.83 (1H, s), 8.99 (1H, dd, J_1 = 7.5 Hz, J_2 = 1.2 Hz), 8.90 (1H, dd, J_1 = 4.2 Hz, J_2 = 1.6 Hz), 8.23 (1H, dd, J_1 = 8.2 Hz, J_2 = 1.5 Hz), 8.18 (2H, d, J = 8.4 Hz), 7.79 (2H, d, J = 8.4 Hz), 7.64–7.59 (4H, m), 7.52 (1H, dd, J_1 = 8.2 Hz, J_2 = 4.2 Hz), 7.33 (2H, d, J = 8.1 Hz), 2.69 (2H, t, J = 7.6 Hz), 1.69–1.67 (4H, m), 1.39–1.32 (6H, m), 0.92 (3H, t, J = 6.7 Hz). $^{13}C\{1H\}$ NMR (~101 MHz, $CDCl_3$): δ_C 165.3, 148.3, 144.6, 143.1, 138.8, 137.3, 136.4, 134.7, 133.5, 129.1, 128.0, 127.8, 127.5, 127.2, 127.1, 121.7, 121.7, 116.6, 35.7, 31.9, 31.5, 29.4, 29.2, 22.7, 14.2. HRMS (ESI): *m/z* $[M+H]^+$ calcd for $C_{29}H_{31}N_2O$: 423.2436 found, 423.2447.



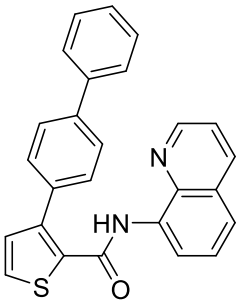
3k

4-Methoxy-*N*-(quinolin-8-yl)-[1,1':3',1''-terphenyl]-2'-carboxamide (5a): Following the general procedure B, **5a** was obtained after purification by column chromatography on silica gel (EtOAc:Hexane = 20:80) as brown sticky solid (72 mg, 88%, 0.2 mmol scale); R_f = 0.3 (EtOAc:Hexane = 20:80); IR (DCM): 3339, 1674, 1517, 1472, 1249 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ_H 9.68 (1H, s), 8.61–8.58 (2H, m), 8.06 (1H, dd, J_1 = 8.3 Hz, J_2 = 1.6 Hz), 7.60–7.56 (3H, m), 7.53–7.43 (6H, m), 7.35 (1H, dd, J_1 = 8.3 Hz, J_2 = 4.2 Hz), 7.30–7.26 (2H, m), 7.20–7.18 (1H, m), 6.83 (2H, dt, J_1 = 8.8 Hz, J_2 = 2.0 Hz), 3.39 (3H, s). $^{13}C\{^1H\}$ NMR (~101 MHz, $CDCl_3$): δ_C 167.7, 158.9, 147.8, 140.5, 140.4, 140.1, 138.3, 136.0, 136.0, 134.3, 132.8, 129.8, 129.4, 129.3, 129.1, 128.7, 128.2, 127.6, 127.3, 127.2, 121.5, 121.3, 116.4, 113.7, 55.1. HRMS (ESI): *m/z* $[M+H]^+$ calcd for $C_{29}H_{23}N_2O_2$: 431.1760 found, 431.1748.



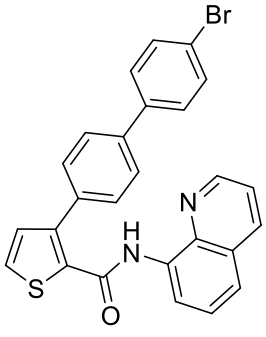
5a

3-([1,1'-Biphenyl]-4-yl)-*N*-(quinolin-8-yl)thiophene-2-carboxamide (5aa): Following general procedure B, the compound **5aa** was obtained after purification by column chromatography on silica gel (EtOAc:hexane = 20:80) as a colourless solid (65 mg, 80%, 0.2 mmol scale); R_f = 0.5 (EtOAc:hexane = 20:80); mp: 149-151 ^oC; IR (DCM): 3297, 1648, 1527, 1480, 1271 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ_H 10.22 (1H, s), 8.88 (1H, dd, J_1 = 7.7 Hz, J_2 = 1.1 Hz), 8.14 (1H, dd, J_1 = 4.2 Hz, J_2 = 1.6 Hz), 8.02 (1H, dd, J_1 = 8.3 Hz, J_2 = 1.6 Hz), 7.71–7.59 (7H, m), 7.56–7.42 (5H, m), 7.19–7.16 (2H, m); $^{13}C\{^1H\}$ NMR (~101 MHz, $CDCl_3$): δ_C 160.7, 147.6, 142.7, 141.3, 140.6, 138.4, 135.8, 135.8, 134.5, 134.1, 131.4, 130.1, 129.5, 129.0, 127.8, 127.7, 127.6, 127.3, 127.1, 121.5, 121.3, 116.4; HRMS (ESI): *m/z* $[M+H]^+$ calcd for $C_{26}H_{19}N_2OS$: 407.1218 found, 407.1202.



5aa

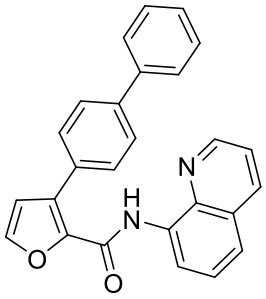
3-(4'-Bromo-[1,1'-biphenyl]-4-yl)-*N*-(quinolin-8-yl)thiophene-2-carboxamide (5ab): Following the general procedure B, The compound **5ab** was obtained after purification by column chromatography on silica gel (EtOAc:hexanes = 10:90) as a colourless solid; (95 mg, 98%, 0.2 mmol scale); R_f = 0.5 (EtOAc:hexane = 10:90); mp: 185-187 ^oC; IR (DCM): 3293, 2930, 1652, 1520, 805 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ_H 10.14 (1H, s), 8.84 (1H, d, J = 7.5 Hz), 8.09 (1H, dd, J_1 = 4.1 Hz, J_2 = 1.4 Hz), 8.02 (1H, dd, J_1 = 8.3 Hz, J_2 = 1.2 Hz), 7.63 (4H, s), 7.59-7.57 (3H, m), 7.53-7.49 (1H, m), 7.45-7.43 (3H, m), 7.18 (1H, dd, J_1 = 8.3 Hz, J_2 = 4.2 Hz), 7.14 (1H, d, J = 5.0 Hz); $^{13}C\{^1H\}$ NMR (~101 MHz, $CDCl_3$): δ_C 160.5, 147.4, 142.5, 139.9, 139.4,



5ab

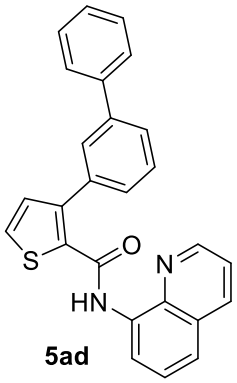
138.3, 135.9, 135.7, 134.6, 134.4, 132.0, 131.2, 130.2, 129.5, 128.6, 127.7, 127.5, 127.3, 121.9, 121.5, 121.2, 116.4; HRMS (ESI): *m/z* $[M+H]^+$ calcd for $C_{26}H_{18}BrN_2OS$: 485.0323 found, 485.0305.

3-([1,1'-Biphenyl]-4-yl)-*N*-(quinolin-8-yl)furan-2-carboxamide (5ac): Following the general procedure B, **5ac** was obtained after purification by column chromatography on silica gel (EtOAc:Hexane = 20:80) as colourless solid (73 mg, 93%, 0.2 mmol scale); R_f = 0.5 (EtOAc:Hexane = 20:80); mp: 154-156 °C; IR (DCM): 3296, 1648, 1527, 1271, 744 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ_H 10.23 (1H, s), 8.89 (1H, d, *J* = 7.6 Hz), 8.14 (1H, d, *J* = 4.0 Hz), 8.01 (1H, d, *J* = 8.2 Hz), 7.70 (2H, d, *J* = 8.0 Hz), 7.66–7.59 (5H, m), 7.55–7.40 (5H, m), 7.18–7.15 (2H, m); $^{13}C\{^1H\}$ NMR (~101 MHz, $CDCl_3$): δ_C 160.7, 147.7, 142.7, 141.3, 140.6, 138.4, 135.8, 135.8, 134.5, 134.1, 131.4, 130.1, 129.5, 129.0, 127.8, 127.7, 127.7, 127.3, 127.1, 121.6, 121.3, 116.4. HRMS (ESI): *m/z* $[M+H]^+$ calcd for $C_{26}H_{19}N_2O_2$: 391.1447 found, 391.1447.



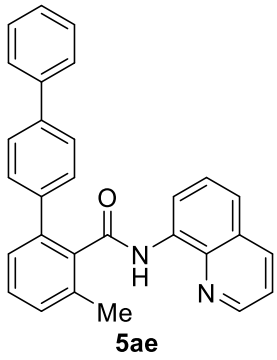
5ac

3-([1,1'-Biphenyl]-3-yl)-*N*-(quinolin-8-yl)thiophene-2-carboxamide (5ad): Following general procedure B, the compound **5ad** was obtained after purification by column chromatography on silica gel (EtOAc:hexane = 20:80) as a yellow solid (51 mg, 63%, 0.2 mmol scale); R_f = 0.5 (EtOAc:hexane = 20:80); mp: 175-177 °C; IR (DCM): 3302, 1652, 1528, 1268, 753 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ_H 10.18 (1H, s), 8.87 (1H, d, *J* = 7.7 Hz), 8.17 (1H, d, *J* = 3.7 Hz), 8.02 (1H, d, *J* = 8.2 Hz), 7.83 (1H, s), 7.72 (1H, d, *J* = 7.0 Hz), 7.60 (1H, d, *J* = 5.0 Hz), 7.55-7.52 (5H, m), 7.46–7.34 (4H, m), 7.24 (1H, dd, J_1 = 8.2 Hz, J_2 = 4.2 Hz), 7.18 (1H, d, *J* = 5.0 Hz); $^{13}C\{^1H\}$ NMR (~101 MHz, $CDCl_3$): δ_C 160.7, 147.7, 142.9, 142.2, 140.7, 138.5, 136.0, 135.8, 135.7, 134.5, 131.4, 129.6, 128.8, 128.5, 128.4, 127.7, 127.5, 127.3, 127.2, 127.1, 121.5, 121.3, 116.4. HRMS (ESI): *m/z* $[M+H]^+$ calcd for $C_{26}H_{19}N_2OS$: 407.1218 found, 407.1223.



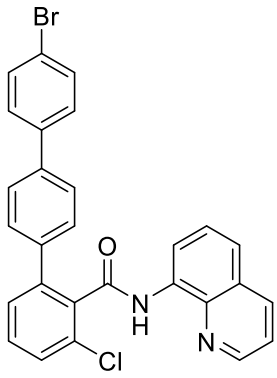
5ad

3-Methyl-*N*-(quinolin-8-yl)-[1,1':4',1''-terphenyl]-2-carboxamide (5ae): Following general procedure B, the compound **5ae** was obtained after purification by column chromatography on silica gel (EtOAc:hexane = 20:80) as a colourless solid (64 mg, 78%, 0.2 mmol scale); R_f = 0.6 (EtOAc:hexane = 20:80); mp: 178-180 °C; IR (DCM): 3345, 3050, 1666, 1516, 1261 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ_H 9.76 (1H, s), 8.86 (1H, d, J = 7.4 Hz), 8.63 (1H, d, J = 3.2 Hz), 8.07 (1H, d, J = 8.2 Hz), 7.67 (2H, d, J = 8.1 Hz), 7.55 (1H, t, J = 7.8 Hz), 7.51–7.46 (4H, m), 7.44–7.34 (7H, m), 7.33–7.28 (1H, m), 2.61 (3H, s); $^{13}C\{^1H\}$ NMR (~101 MHz, $CDCl_3$): δ_C 168.4, 148.0, 140.6, 140.0, 139.4, 139.3, 138.4, 136.8, 136.1, 136.0, 134.4, 129.7, 129.4, 129.1, 128.6, 127.8, 127.7, 127.3, 127.2, 127.0, 127.0, 121.9, 121.5, 116.6, 19.9. HRMS (ESI): *m/z* $[M+H]^+$ calcd for $C_{29}H_{23}N_2O$: 415.1810 found, 415.1822.



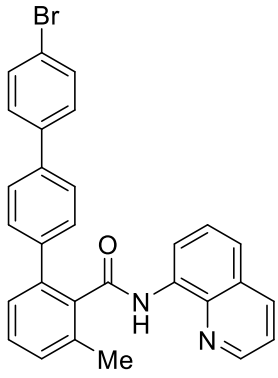
5ae

4''-Bromo-3-chloro-*N*-(quinolin-8-yl)-[1,1':4',1''-terphenyl]-2-carboxamide (5af): Following the general procedure B, **5af** was obtained after purification by column chromatography on silica gel (EtOAc:Hexane = 20:80) as a colourless solid (47 mg, 46%, 0.2 mmol scale); R_f = 0.5 (EtOAc:Hexane = 20:80); mp: 188-190 °C; IR (DCM): 3334, 1677, 1511, 1468, 1261 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ_H 9.91 (1H, s), 8.83 (1H, d, J = 7.1 Hz), 8.69–8.68 (1H, m), 8.11 (1H, d, J = 8.3 Hz), 7.64 (2H, d, J = 7.6 Hz), 7.56–7.42 (9H, m), 7.39 (1H, dd, J_1 = 8.2 Hz, J_2 = 4.2 Hz), 7.30 (2H, d, J = 8.9 Hz); $^{13}C\{^1H\}$ NMR (~101 MHz, $CDCl_3$): δ_C 165.2, 148.2, 141.2, 139.4, 139.3, 138.5, 138.4, 136.3, 136.0, 134.1, 132.0, 131.8, 130.4, 129.2, 128.9, 128.7, 128.6, 127.9, 127.3, 126.9, 122.2, 121.7, 121.6, 116.9. HRMS (ESI): *m/z* $[M+H]^+$ calcd for $C_{28}H_{19}BrClN_2O$: 513.0369 found, 513.0376.



5af

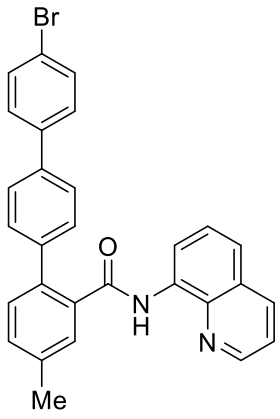
4''-Bromo-3-methyl-*N*-(quinolin-8-yl)-[1,1':4',1''-terphenyl]-2-carboxamide (5ag): Following the general procedure B, **5ag** was obtained after purification by column chromatography on silica gel (EtOAc:Hexane = 20:80) as a colourless solid (72 mg, 73%, 0.2 mmol scale); R_f = 0.5 (EtOAc:Hexane = 20:80); mp: 166-168 °C; IR (DCM): 3341, 3053, 1673, 1522, 1266 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ_H 9.76 (1H, s), 8.85 (1H, d, J = 7.5 Hz), 8.63–8.62 (1H, m), 8.07 (1H, d, J = 8.2 Hz), 7.65 (2H, d, J = 7.5 Hz), 7.54 (1H, t, J = 8.0 Hz), 7.49–7.39 (6H, m), 7.37–7.32 (3H, m), 7.25 (2H, d, J = 7.8 Hz), 2.60 (3H, s); $^{13}C\{^1H\}$



5ag

NMR (~101 MHz, $CDCl_3$): δ_C 168.4, 148.0, 139.8, 139.5, 139.1, 138.8, 138.4, 136.8, 136.1, 136.0, 134.4, 131.7, 129.8, 129.4, 129.3, 128.5, 127.8, 127.6, 127.3, 126.8, 121.9, 121.5, 121.5, 116.6, 19.9. HRMS (ESI): *m/z* $[M+H]^+$ calcd for $C_{29}H_{22}BrN_2O$: 493.0916 found, 493.0916.

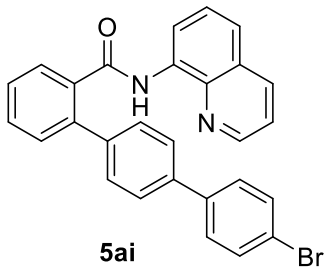
4''-Bromo-4-methyl-*N*-(quinolin-8-yl)-[1,1':4',1''-terphenyl]-2-carboxamide (5ah):



5ah

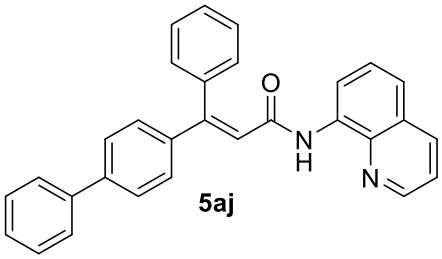
Following the general procedure B, The compound **(5ah)** was obtained after purification by column chromatography on silica gel (EtOAc:hexanes = 10:90) as a colourless solid (106 mg, 57%, 0.38 mmol scale); R_f = 0.5 (EtOAc:hexane = 10:90); mp: 208-210 ^oC; IR (DCM): 3057, 1265, 727 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ_H 9.82 (1H, s), 8.82 (1H, d, J = 7.3 Hz), 8.44 (1H, dd, J_1 = 4.1 Hz, J_2 = 1.4 Hz), 8.04 (1H, dd, J_1 = 8.3 Hz, J_2 = 1.2 Hz), 7.75 (1H, s), 7.57-7.38 (11H, m), 7.28-7.21 (2H, m), 2.48 (3H, s); $^{13}C\{^1H\}$ NMR (~101 MHz, $CDCl_3$): δ_C 167.9, 147.7, 139.5, 139.3, 139.0, 138.4, 137.8, 136.8, 135.9, 135.8, 134.5, 131.7, 131.4, 130.5, 129.9, 129.6, 128.5, 127.7, 127.3, 126.9, 121.5, 121.4, 121.3, 116.3, 21.1; HRMS (ESI): *m/z* $[M+H]^+$ calcd for $C_{29}H_{22}BrN_2O$: 493.0916; found: 493.0936.

4''-Bromo-*N*-(quinolin-8-yl)-[1,1':4',1''-terphenyl]-2-carboxamide (5ai): Following general procedure B, the compound **5ai** was obtained after purification by column chromatography on silica gel (EtOAc:hexane = 20:80) as a colourless solid (53 mg, 53%, 0.2 mmol scale); R_f = 0.5 (EtOAc:hexane = 20:80); mp 151-153 ^oC; IR (DCM): 3321, 1671, 1525, 1265, 735 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ_H 9.89 (1H, s), 8.85 (1H, dd, J_1 = 7.6 Hz, J_2 = 1.1 Hz), 8.49 (1H, dd, J_1 = 4.2 Hz, J_2 = 1.6 Hz), 8.08 (1H, dd, J_1 = 8.3 Hz, J_2 = 1.6 Hz), 7.98–7.96 (1H, m), 7.64–7.60 (3H, m), 7.57-7.53 (3H, m), 7.52–7.47 (5H, m), 7.32–7.26 (3H, m); $^{13}C\{^1H\}$ NMR (~101 MHz, $CDCl_3$): δ_C 167.8, 147.8, 139.7, 139.5, 139.4, 139.2, 138.4, 136.0, 134.5, 131.8, 130.7, 130.6, 129.6, 129.4, 128.6, 127.8, 127.7, 127.3, 127.0, 121.7, 121.5, 121.4, 116.4. HRMS (ESI): *m/z* $[M+H]^+$ calcd for $C_{28}H_{20}BrN_2O$: 479.0759 found, 479.0756.



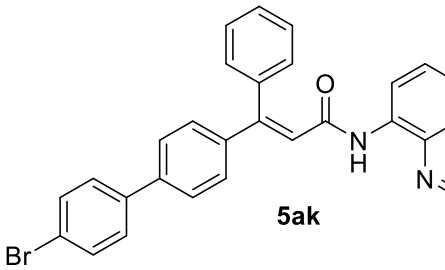
5ai

(*E*)-3-([1,1'-Biphenyl]-4-yl)-3-phenyl-*N*-(quinolin-8-yl)acrylamide (5aj): Following the general procedure B, **5aj** was obtained after purification by column chromatography on silica gel (EtOAc:Hexane = 20:80) as a colourless solid (56 mg, 66%, 0.2 mmol scale); R_f = 0.5 (EtOAc:Hexane = 20:80); mp: 167-169 ^oC; IR (DCM): 3336, 1658, 1535, 1275, 765 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ_H 9.89 (1H, s), 8.86 (1H, d, J = 7.5 Hz), 8.49 (1H, d, J = 4.1 Hz), 8.08 (1H, d, J = 8.2 Hz), 7.63 (2H, d, J = 7.8 Hz), 7.56–7.38 (14H, m), 7.30 (1H, dd, J_1 = 8.3 Hz, J_2 = 4.2 Hz) 6.68 (1H, s); $^{13}C\{^1H\}$ NMR (~101 MHz, $CDCl_3$): δ_C 164.7, 152.0, 147.8, 141.5, 141.4, 140.6, 138.4, 137.3, 136.1, 134.6, 130.5, 129.2, 128.8, 128.5, 128.5, 127.8, 127.5, 127.4, 127.2, 127.1, 122.9, 121.4, 116.5. HRMS (ESI): *m/z* $[M+H]^+$ calcd for $C_{30}H_{23}N_2O$: 427.1810 found, 427.1793.



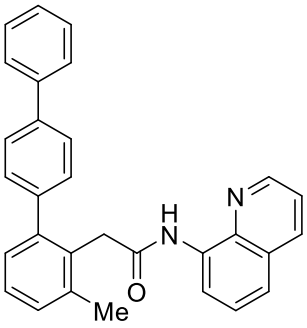
5aj

(*E*)-3-(4'-Bromo-[1,1'-biphenyl]-4-yl)-3-phenyl-*N*-(quinolin-8-yl)acrylamide (**5ak**): Following the general procedure B, **5ak** was obtained after purification by column chromatography on silica gel (EtOAc:Hexane = 20:80) as a colourless solid (70 mg, 69%, 0.2 mmol scale); R_f = 0.5 (EtOAc:Hexane = 20:80); mp: 184-186 ^oC; IR (DCM): 3329, 3047, 1665, 1524, 1264 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ_H 9.87 (1H, s), 8.83 (1H, d, J = 7.4 Hz), 8.50–8.49 (1H, m), 8.09 (1H, d, J = 8.2 Hz), 7.58–739 (15H, m), 7.32 (1H, dd, J_1 = 8.2 Hz, J_2 = 4.1 Hz), 6.68 (1H, s); $^{13}C\{^1H\}$ NMR (~101 MHz, $CDCl_3$): δ_C 164.5, 152.0, 147.8, 141.4, 140.1, 139.5, 138.3, 137.8, 136.1, 134.6, 131.9, 130.5, 129.3, 128.7, 128.5, 128.5, 127.8, 127.4, 126.9, 122.8, 121.8, 121.5, 121.4, 116.5. HRMS (ESI): *m/z* $[M+H]^+$ calcd for $C_{30}H_{22}BrN_2O$: 505.0916 found, 505.0896.



5ak

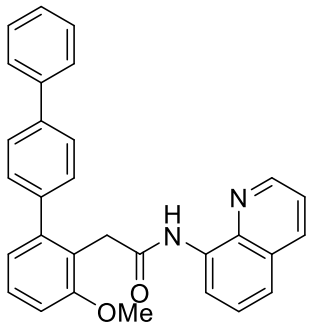
2-(3-Methyl-[1,1':4',1''-terphenyl]-2-yl)-*N*-(quinolin-8-yl)acetamide (5al): Following the general procedure B, **5al** was obtained after purification by column chromatography on silica gel (EtOAc:Hexane = 20:80) as a colourless solid (78 mg, 91%, 0.2 mmol scale); R_f = 0.5 (EtOAc:Hexane = 20:80); mp: 149-151 ^oC; IR (DCM): 3343, 3051, 1682, 1524, 1476 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ_H 9.87 (1H, s), 8.83-8.82 (1H, m), 8.67 (1H, d, J = 3.3 Hz), 8.14 (1H, d, J = 8.2 Hz), 7.64–7.53 (8H, m), 7.51–7.46 (2H, m), 7.44-7.28 (5H, m), 4.00 (2H, s), 2.52 (3H, s); $^{13}C\{^1H\}$ NMR (~101 MHz, $CDCl_3$): δ_C 169.7, 148.2, 143.3, 140.8, 140.7,



5al

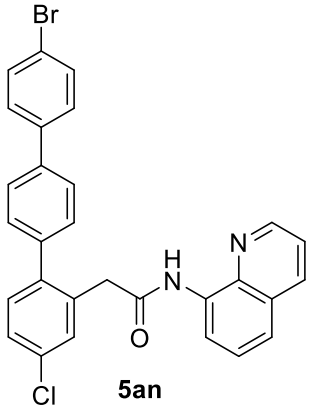
140.0, 138.5, 138.3, 136.2, 134.5, 131.1, 130.1, 129.8, 128.8, 128.4, 127.9, 127.4, 127.3, 127.1, 127.1, 121.6, 116.3, 40.2, 20.6. HRMS (ESI): *m/z* $[M+H]^+$ calcd for $C_{30}H_{25}N_2O$: 429.1967 found, 429.1951.

2-(3-Methoxy-[1,1':4',1''-terphenyl]-2-yl)-*N*-(quinolin-8-yl)acetamide (5am): Following general procedure B, the compound **5am** was obtained after purification by column chromatography on silica gel (EtOAc:hexane = 20:80) as a colourless solid (85 mg, 96%, 0.2 mmol scale); R_f = 0.4 (EtOAc:hexane = 20:80); mp 193-195 °C; IR (DCM): 1682, 1530, 1477, 1260, 756 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ_H 10.35 (1H, s), 8.87 (1H, d, *J* = 7.6 Hz), 8.77- 8.76 (1H, m), 8.14 (1H, d, *J* = 8.2 Hz), 7.71–7.66 (4H, m), 7.62 (2H, d, *J* = 7.4 Hz), 7.58–7.55 (1H, m), 7.51–7.47 (3H, m), 7.44–7.37 (3H, m), 7.10 (1H, d, *J* = 7.7 Hz), 7.04 (1H, d, *J* = 8.3 Hz), 4.01 (3H, s), 3.96 (2H, s); $^{13}C\{^1H\}$ NMR (~101 MHz, $CDCl_3$): δ_C 170.3, 157.9, 148.0, 144.2, 140.8, 140.1, 139.9, 138.6, 136.2, 135.0, 130.1, 128.8, 128.1, 128.0, 127.5, 127.3, 127.2, 127.0, 122.9, 121.7, 121.5, 121.3, 116.5, 109.5, 55.9, 37.4. HRMS (ESI): *m/z* $[M+H]^+$ calcd for $C_{30}H_{25}N_2O_2$: 445.1916 found, 445.1901.



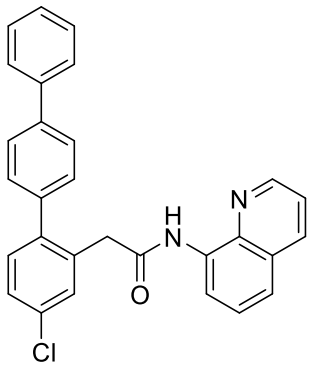
5am

2-(4''-Bromo-4-chloro-[1,1':4',1''-terphenyl]-2-yl)-*N*-(quinolin-8-yl)acetamide (5an): Following general procedure B, the compound **5an** was obtained after purification by column chromatography on silica gel (EtOAc:hexane = 20:80) as a colourless solid (85 mg, 81%, 0.2 mmol scale); R_f = 0.4 (EtOAc:hexane = 20:80); mp: 178-180 °C; IR (DCM): 3339, 1685, 1532, 1265, 731 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ_H 9.79 (1H, s), 8.74 (1H, d, *J* = 6.7 Hz), 8.68 (1H, d, *J* = 4.0 Hz), 8.14 (1H, d, *J* = 8.2 Hz), 7.59–7.52 (7H, m), 7.47–7.39 (6H, m), 7.33 (1H, d, *J* = 8.2 Hz), 3.87 (2H, s); $^{13}C\{^1H\}$ NMR (~101 MHz, $CDCl_3$): δ_C 168.8, 148.2, 140.6, 139.4, 139.4, 139.1, 138.3, 136.3, 134.3, 134.2, 133.8, 131.9, 131.6, 130.8, 129.8, 128.6, 127.9, 127.6, 127.4, 127.0, 121.8, 121.7, 121.6, 116.4, 42.5. HRMS (ESI): *m/z* $[M+H]^+$ calcd for $C_{29}H_{21}BrClN_2O$: 527.0526 found, 527.0505.



5an

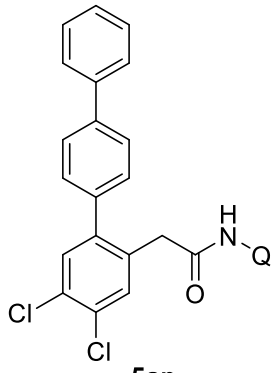
2-(4-Chloro-[1,1':4',1''-terphenyl]-2-yl)-*N*-(quinolin-8-yl)acetamide (5ao):



5ao

Following the general procedure B, **5ao** was obtained after purification by column chromatography on silica gel (EtOAc:hexanes = 20:80) as a colourless solid (72 mg, 80%, 0.2 mmol scale); R_f = 0.5 (EtOAc:hexane = 20:80); mp: 125-127 ^oC; IR (DCM): 3423, 1696, 1539,760 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ_H 9.76 (1H, s), 8.71 (1H, dd, J_1 = 7.1 Hz, J_2 = 1.4 Hz), 8.64 (1H, dd, J_1 = 4.1 Hz, J_2 = 1.4 Hz), 8.07 (1H, dd, J_1 = 8.3 Hz, J_2 = 1.3 Hz), 7.59-7.22 (15H, m), 3.84 (2H, s); $^{13}C\{^1H\}$ NMR (~101 MHz, $CDCl_3$): δ_C 168.8, 148.1, 140.7, 140.4, 140.3, 138.8, 138.2, 136.1, 134.2, 134.2, 133.6, 131.5, 130.6, 129.6, 128.7, 127.8, 127.5, 127.3, 127.2, 127.1, 127.0, 121.6, 121.5, 116.3, 42.4; HRMS (ESI): *m/z* $[M+H]^+$ calcd for $C_{29}H_{22}ClN_2O$: 449.1421; found: 449.1413.

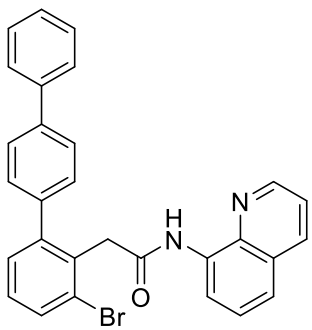
2-(4,5-Dichloro-[1,1':4',1''-terphenyl]-2-yl)-*N*-(quinolin-8-yl)acetamide (5ap):



5ap

Following the general procedure B, **5ap** was obtained after purification by column chromatography on silica gel (EtOAc:hexanes = 20:80) as a colourless solid (240 mg, 66%, 0.75 mmol scale); R_f = 0.5 (EtOAc:hexane = 20:80); mp: 165-167 ^oC; IR (DCM): 3348, 3043, 1683, 1527, 729 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ_H 9.75 (1H, s), 8.70 (1H, dd, J_1 = 6.4 Hz, J_2 = 2.5 Hz), 8.66 (1H, dd, J_1 = 4.2 Hz, J_2 = 1.5 Hz),8.12 (1H, dd, J_1 = 8.3 Hz, J_2 = 1.5 Hz), 7.65 (1H, s), 7.60 (2H, d, J = 8.1 Hz), 7.53-7.47 (5H, m), 7.43-7.37 (6H, m), 3.82 (2H, s); $^{13}C\{^1H\}$ NMR (~101 MHz, $CDCl_3$): δ_C 168.5, 148.2, 142.2, 140.8, 140.3, 138.2, 138.0, 136.2, 134.1, 132.7, 132.5, 131.8, 131.7, 131.2, 129.5, 128.8, 127.8, 127.5, 127.3, 127.3, 127.0, 121.8, 121.6, 116.4, 41.8; HRMS (ESI): *m/z* calcd for $C_{29}H_{21}Cl_2N_2O$: 483.1031; found: 483.1026.

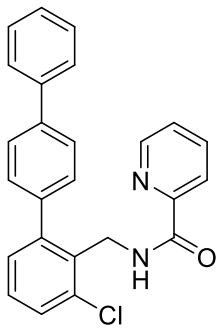
2-(3-Bromo-[1,1':4',1''-terphenyl]-2-yl)-*N*-(quinolin-8-yl)acetamide (5aq): Following general procedure B, the compound **5aq** was obtained after purification by column chromatography on silica gel (EtOAc:hexane = 20:80) as a brown solid (300 mg, 61%, 1 mmol scale); R_f = 0.6 (EtOAc:hexane = 20:80); mp: 138-140 ^oC; IR (DCM): 3342, 1686, 1525, 1265, 732 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ_H 9.87 (1H, s), 8.81–8.79 (1H, m), 8.70 (1H, dd, J_1 = 4.2 Hz, J_2 = 1.6 Hz), 8.15 (1H, dd, J_1 = 8.3 Hz, J_2 = 1.6 Hz), 7.71 (1H, dd, J_1 = 8.0 Hz, J_2 = 1.3 Hz), 7.62–7.56 (5H, m), 7.54–7.50 (3H, m), 7.46–7.41 (3H, m), 7.39–7.29 (3H, m), 4.11 (2H, s);



5aq

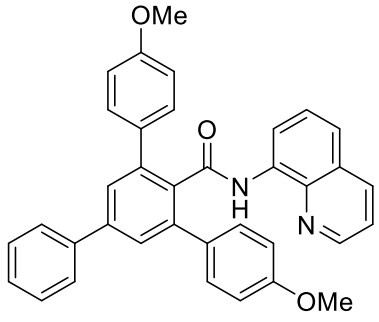
$^{13}C\{^{1}H\}$ NMR (~101 MHz, $CDCl_3$): δ_C 168.4, 148.1, 145.1, 140.5, 140.4, 139.8, 138.3, 136.2, 134.4, 132.7, 132.3, 129.5, 129.5, 128.8, 128.6, 127.9, 127.4, 127.1, 127.0, 126.9, 121.5, 121.5, 116.3, 43.1. HRMS (ESI): *m/z* $[M+H]^+$ calcd for $C_{29}H_{22}BrN_2O$: 493.0916 found, 493.0917.

***N*-((3-Chloro-[1,1':4',1''-terphenyl]-2-yl)methyl)picolinamide (5ar):** Following general procedure B, the compound **5ar** was obtained after purification by column chromatography on silica gel (EtOAc:hexane = 20:80) as a brown coloured solid (71 mg, 89%, 0.2 mmol scale); R_f = 0.6 (EtOAc:hexane = 20:80); mp: 143-145 °C; IR (DCM): 3389, 1675, 1513, 1268, 723 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 8.55–8.53 (1H, m), 8.25–8.20 (2H, m), 7.84 (1H, td, J_1 = 7.7 Hz, J_2 = 1.7 Hz), 7.68–7.65 (4H, m), 7.50–7.34 (8H, m), 7.31–7.28 (1H, m), 4.78 (2H, d, J = 5.2 Hz); $^{13}C\{^{1}H\}$ NMR (~101 MHz, $CDCl_3$): δ_C 163.6, 149.8, 148.1, 144.8, 140.5, 139.0, 137.3, 136.0, 132.8, 129.5, 129.1, 129.1, 128.8, 128.8, 127.4, 127.1, 126.1, 122.2, 39.7; HRMS (ESI): *m/z* $[M+H]^+$ calcd for $C_{25}H_{20}ClN_2O$: 399.1264 found, 399.1273.



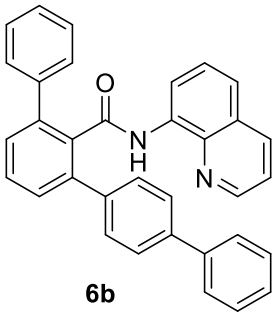
11

4,4''-Dimethoxy-5'-phenyl-*N*-(quinolin-8-yl)-[1,1':3',1''-terphenyl]-2'-carboxamide (6a): Following the general procedure B, **6a** was obtained after purification by column chromatography on silica gel (EtOAc:Hexane = 20:80) as colourless solid (85 mg, 80%, 0.2 mmol scale); R_f = 0.3 (EtOAc:Hexane = 20:80); mp: 170-172 °C; IR (DCM): 3343, 1674, 1517, 1248, 743 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 9.75 (1H, s), 8.66–8.62 (2H, m), 8.07 (1H, d, J = 8.2 Hz), 7.74 (2H, d, J = 7.6 Hz), 7.70 (2H, s), 7.59 (4H, d, J = 7.7 Hz), 7.54–7.44 (5H, m), 7.36 (1H, dd, J_1 = 7.2 Hz, J_2 = 4.1 Hz), 6.85 (4H, d, J = 7.8 Hz), 3.70 (6H, s). $^{13}C\{^{1}H\}$ NMR (~101 MHz, $CDCl_3$): δ_C 167.9, 159.0, 147.8, 142.1, 140.7, 140.2, 138.3, 136.0, 134.9, 134.4, 132.8, 129.8, 128.9, 127.9, 127.8, 127.7, 127.3, 127.2, 121.5, 121.4, 116.4, 113.7, 55.1. HRMS (ESI): *m/z* $[M+H]^+$ calcd for $C_{36}H_{29}N_2O_3$: 537.2178 found, 537.2187.



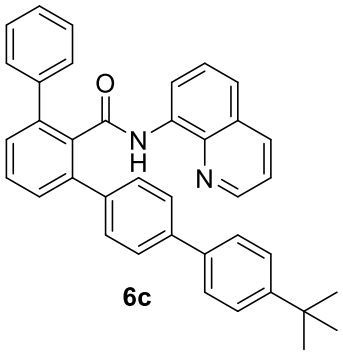
6a

***N*-(Quinolin-8-yl)-[1,1':3',1'':4'',1'''-quaterphenyl]-2'-carboxamide (6b):** Following general procedure B, the compound **6b** was obtained after purification by column chromatography on silica gel (EtOAc:hexane = 20:80) as a colourless solid (68 mg, 72%, 0.2 mmol scale); R_f = 0.5 (EtOAc:hexane = 20:80); mp 198-200 °C; IR (DCM): 3339, 1676, 1522, 1261, 760 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ_H 9.66 (1H, s), 8.56–8.52 (2H, m), 8.03 (1H, dd, J_1 = 8.3 Hz, J_2 = 1.5 Hz), 7.63–7.37 (12H, m), 7.35–7.24 (7H, m), 7.16 (1H, t, J = 7.3 Hz); $^{13}C\{^1H\}$ NMR (~101 MHz, $CDCl_3$): δ_C 167.6, 147.8, 140.7, 140.7, 140.4, 140.2, 140.1, 139.4, 138.3, 136.1, 136.0, 134.3, 129.5, 129.5, 129.4, 129.2, 128.7, 128.6, 128.3, 127.7, 127.4, 127.2, 127.0, 127.0, 121.6, 121.4, 116.5. HRMS (ESI): *m/z* $[M+H]^+$ calcd for $C_{34}H_{25}N_2O$: 477.1967 found, 477.1948.



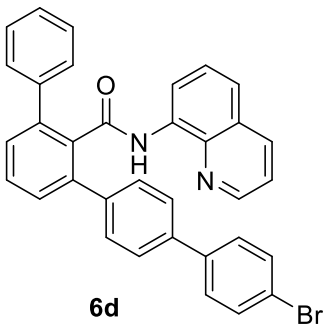
6b

4'''-(*Tert*-butyl)-*N*-(quinolin-8-yl)-[1,1':3',1'':4'',1'''-quaterphenyl]-2'-carboxamide (6c): Following general procedure B, the compound **6c** was obtained after purification by column chromatography on silica gel (EtOAc:hexane = 20:80) as a brown solid (63 mg, 59%, 0.2 mmol scale); R_f = 0.5 (EtOAc:hexane = 20:80); mp: 222-224 °C; IR (DCM): 3339, 1675, 1518, 1263, 739 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ_H 9.69 (1H, s), 8.59 (1H, dd, J_1 = 4.2 Hz, J_2 = 1.6 Hz), 8.56–8.54 (1H, m), 8.05 (1H, dd, J_1 = 8.3 Hz, J_2 = 1.6 Hz), 7.64–7.54 (6H, m), 7.51–7.46 (3H, m), 7.44–7.41 (6H, m), 7.34 (1H, dd, J_1 = 8.3 Hz, J_2 = 4.2 Hz), 7.30–7.27 (2H, m), 7.19 (1H, t, J = 7.4 Hz), 1.35 (9H, s); $^{13}C\{^1H\}$ NMR (~101 MHz, $CDCl_3$): δ_C 167.6, 150.2, 147.8, 140.7, 140.4, 140.2, 140.0, 139.1, 138.3, 137.8, 136.1, 136.0, 134.3, 129.5, 129.4, 129.1, 128.7, 128.3, 127.7, 127.4, 127.2, 126.9, 126.7, 125.6, 121.6, 121.4, 116.5, 34.5, 31.4. HRMS (ESI): *m/z* $[M+H]^+$ calcd for $C_{38}H_{33}N_2O$: 533.2593 found, 533.2567.



6c

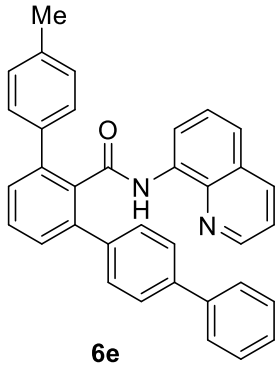
4'''-Bromo-*N*-(quinolin-8-yl)-[1,1':3',1'':4'',1'''-quaterphenyl]-2'-carboxamide (6d): Following general procedure B, the compound **6d** was obtained after purification by column chromatography on silica gel (EtOAc:hexane = 20:80) as a brown solid (76 mg, 68%, 0.2 mmol scale); R_f = 0.5 (EtOAc:hexane = 20:80); mp: 165-167 °C; IR (DCM): 3371, 1676, 1505, 1267, 739 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ_H 9.68 (1H, s), 8.58 (1H, dd, J_1 = 4.2 Hz, J_2 = 1.6 Hz), 8.55 (1H, dd, J_1 = 5.8 Hz, J_2 = 3.2 Hz), 8.06 (1H, dd, J_1 = 8.3 Hz, J_2 = 1.6 Hz), 7.65–7.57 (5H, m), 7.54–7.43 (8H, m), 7.36–7.26 (5H, m), 7.18 (1H, t, J = 7.4 Hz); $^{13}C\{^1H\}$ NMR (~101



6d

MHz, $CDCl_3$): δ_C 167.5, 147.8, 140.7, 140.3, 140.0, 139.8, 139.6, 138.9, 138.3, 136.1, 136.0, 134.3, 131.7, 129.6, 129.5, 129.4, 129.3, 128.7, 128.6, 128.2, 127.6, 127.4, 127.2, 126.8, 121.6, 121.5, 121.4, 116.5; HRMS (ESI): *m/z* $[M+H]^+$ calcd for $C_{34}H_{24}BrN_2O$: 555.1072 found, 555.1080.

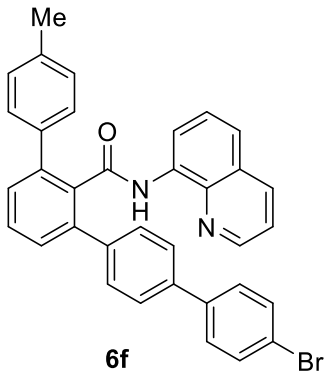
4-Methyl-*N*-(quinolin-8-yl)-[1,1':3',1'':4'',1'''-quaterphenyl]-2'-carboxamide (6e):



6e

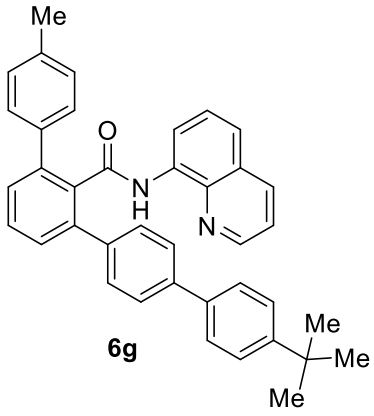
Following the general procedure, the compound **6e** was obtained after purification by column chromatography on silica gel (EtOAc:hexane = 20:80) as a brown colour solid (83 mg, 85%, 0.2 mmol scale); R_f = 0.5 (EtOAc:hexane = 20:80); mp: 180-182 ^oC; IR (DCM): 3341, 1676, 1521, 1263, 736 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ_H 9.77 (1H, s), 8.66–8.60 (2H, m), 8.03 (1H, d, *J* = 8.2 Hz), 7.70 (2H, d, *J* = 7.9 Hz), 7.63 (1H, t, *J* = 7.5 Hz), 7.57–7.31 (14H, m), 7.14 (2H, d, *J* = 7.6 Hz), 2.27 (3H, s); $^{13}C\{^1H\}$- NMR (~101 MHz, $CDCl_3$): δ_C 167.7, 147.8, 140.6, 140.5, 140.0, 140.0, 139.4, 138.3, 137.4, 137.0, 136.0, 135.9, 134.3, 129.5, 129.4, 129.2, 129.1, 129.0, 128.6, 128.5, 127.6, 127.1, 127.0, 126.9, 121.5, 121.3, 116.5, 21.1; HRMS (ESI): *m/z* $[M+H]^+$ calcd for $C_{35}H_{27}N_2O$: 491.2123 found, 491.2105.

4'''-Bromo-4-methyl-*N*-(quinolin-8-yl)-[1,1':3',1'':4'',1'''-quaterphenyl]-2'-carboxamide (6f): Following general procedure B, the compound **6f** was obtained after purification by column chromatography on silica gel (EtOAc:hexane = 20:80) as a yellow solid (75 mg, 67%, 0.2 mmol scale); R_f = 0.5 (EtOAc:hexane = 20:80); mp 202-204 ^oC; IR (DCM): 3348, 1681, 1507, 1266, 728 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ_H 9.68 (1H, s), 8.59–8.56 (2H, m), 8.06 (1H, d, *J* = 8.2 Hz), 7.64–7.85 (3H, m), 7.51–7.42 (10H, m), 7.35–7.28 (3H, m), 7.09 (2H, d, *J* = 7.7 Hz), 2.24 (3H, s); $^{13}C\{^1H\}$ NMR (~101 MHz, $CDCl_3$): δ_C 167.7, 147.8, 140.7, 139.9, 139.9, 139.5, 138.8, 138.3, 137.4, 137.1, 136.0, 135.9, 134.3, 131.7, 129.7, 129.4, 129.3, 129.1, 129.0, 128.5, 127.6, 127.2, 126.7, 121.6, 121.4, 121.3, 116.5, 21.1; HRMS (ESI): *m/z* $[M+H]^+$ calcd for $C_{35}H_{26}BrN_2O$: 569.1229 found, 569.1225.



6f

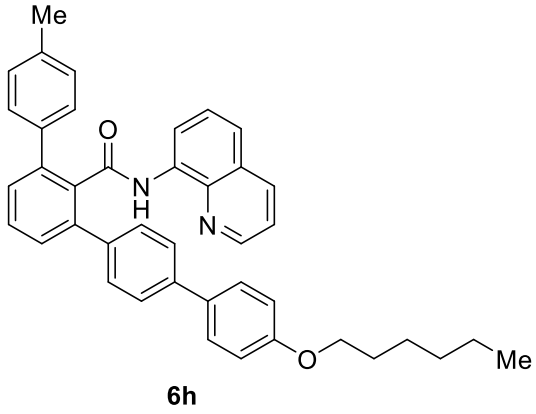
4'''-(*Tert*-butyl)-4-methyl-*N*-(quinolin-8-yl)-[1,1':3',1'':4'',1'''-quaterphenyl]-2'-carboxamide (6g): Following general procedure B, the compound **6g** was obtained after



6g

purification by column chromatography on silica gel (EtOAc:hexane = 20:80) as a yellow solid (95 mg, 87%, 0.2 mmol scale); R_f = 0.6 (EtOAc:hexane = 20:80); mp 194-196 ^oC; IR (DCM): 3339, 1675, 1510, 1264, 725 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ_H 9.66 (1H, s), 8.57–8.53 (2H, m), 8.03 (1H, dd, J_1 = 8.2 Hz, J_2 = 1.3 Hz), 7.61–7.55 (3H, m), 7.50–7.39 (8H, m), 7.37 (4H, s), 7.32 (1H, dd, J_1 = 8.3 Hz, J_2 = 4.2 Hz), 7.07 (2H, d, J = 8.0 Hz), 2.22 (3H, s), 1.32 (9H, s); $^{13}C\{^1H\}$ NMR (~101 MHz, $CDCl_3$): δ_C 167.7, 150.1, 147.8, 140.6, 140.1, 139.9, 139.1, 138.3, 137.7, 137.5, 137.0, 136.0, 135.9, 134.3, 129.5, 129.3, 129.2, 129.0, 129.0, 128.5, 127.6, 127.2, 126.8, 126.6, 125.6, 121.5, 121.3, 116.5, 34.5, 31.3, 21.1; HRMS (ESI): *m/z* $[M+H]^+$ calcd for $C_{39}H_{35}N_2O$: 547.2749 found, 547.2769.

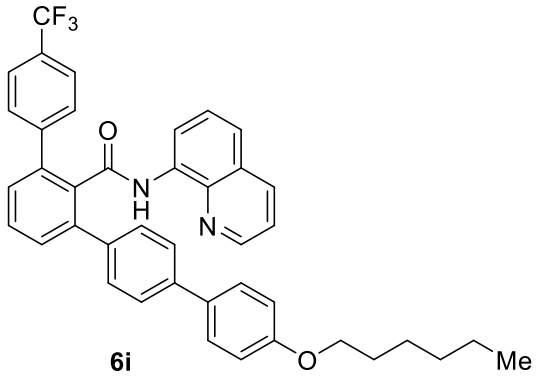
4'''-(Hexyloxy)-4-methyl-*N*-(quinolin-8-yl)-[1,1':3',1'':4'',1'''-quaterphenyl]-2'-carboxamide (6h): Following general procedure B, the compound **6h** was obtained after



6h

purification by column chromatography on silica gel (EtOAc:hexane = 20:80) as a yellow coloured solid (48 mg, 54%, 0.15 mmol scale); R_f = 0.5 (EtOAc:hexane = 20:80); IR (DCM): 3347, 1670, 1491, 1266, 741 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ_H 9.71 (1H, s), 8.61–8.58 (2H, m), 8.04 (1H, dd, J_1 = 8.3 Hz, J_2 = 1.6 Hz), 7.64–7.58 (3H, m), 7.54–7.41 (8H, m), 7.39–7.37 (2H, m), 7.33 (1H, dd, J_1 = 8.2 Hz, J_2 = 4.2 Hz), 7.11 (2H, d, J = 7.9 Hz), 6.91 (2H, dt, J_1 = 8.8 Hz, J_2 = 1.9 Hz), 3.99 (2H, t, J = 6.6 Hz), 2.25 (3H, s), 1.83–1.79 (2H, m), 1.51–1.48 (2H, m), 1.39–1.31 (4H, m), 0.96–0.93 (3H, m); $^{13}C\{^1H\}$ NMR (~101 MHz, $CDCl_3$): δ_C 167.8, 158.7, 147.8, 140.7, 140.2, 139.8, 138.7, 138.4, 137.5, 137.1, 136.0, 136.0, 134.4, 132.9, 129.5, 129.4, 129.2, 129.1, 129.0, 128.6, 128.0, 127.7, 127.2, 126.5, 121.5, 121.3, 116.5, 114.6, 68.1, 31.6, 29.3, 25.8, 22.7, 21.1, 14.1. HRMS (ESI): *m/z* $[M+H]^+$ calcd for $C_{41}H_{39}N_2O_2$: 591.3012 found, 591.3019.

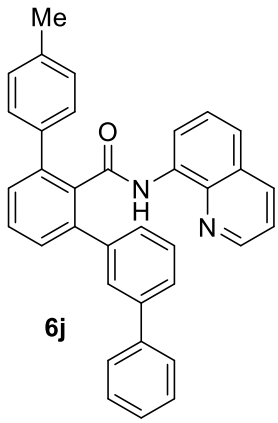
4'''-(Hexyloxy)-*N*-(quinolin-8-yl)-4-(trifluoromethyl)-[1,1':3',1'':4'',1'''-quaterphenyl]-2'-carboxamide (6i): Following general procedure B, the compound **6i** was obtained after



6i

purification by column chromatography on silica gel (EtOAc:hexane = 20:80) as a yellow solid (74 mg, 76%, 0.15 mmol scale); R_f = 0.4 (EtOAc:hexane = 20:80); mp: 180-182 ^oC; IR (DCM): 3344, 1679, 1513, 1327, 1254 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ_H 9.69 (1H, s), 8.57–8.53 (2H, m), 8.06 (1H, dd, J_1 = 8.3 Hz, J_2 = 1.6 Hz), 7.70 (2H, d, J = 8.0 Hz), 7.66–7.59 (4H, m), 7.54 (2H, d, J = 8.2 Hz), 7.49–7.45 (5H, m), 7.38 (2H, dt, J_1 = 8.8 Hz, J_2 = 2.0 Hz), 7.33 (1H, dd, J_1 = 8.3 Hz, J_2 = 4.2 Hz), 6.92 (2H, dt, J_1 = 8.8 Hz, J_2 = 2.0 Hz), 3.99 (2H, t, J = 6.6 Hz), 1.83–1.79 (2H, m), 1.51–1.47 (2H, m), 1.39–1.35 (4H, m), 0.94 (3H, t, J = 7.0 Hz); $^{13}C\{^1H\}$ NMR (~101 MHz, $CDCl_3$): δ_C 167.2, 158.7, 147.9, 144.1, 140.5, 140.0, 139.3, 138.3, 136.1, 136.0, 134.0, 132.8, 130.2, 129.7, 129.6, 129.3, 129.1, 129.1, 128.0, 127.7, 127.2, 126.7 (q, $J_{C\text{-}F}$ = 270.2 Hz), 126.6, 125.2 (q, $J_{C\text{-}F}$ = 3.6 Hz), 121.9, 121.4, 116.6, 114.7, 68.1, 31.6, 29.3, 25.8, 22.6, 14.1. HRMS (ESI): *m/z* $[M+H]^+$ calcd for $C_{41}H_{36}F_3N_2O_2$: 645.2729 found, 645.2754.

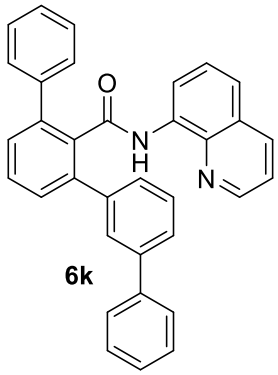
4-Methyl-*N*-(quinolin-8-yl)-[1,1':3',1'':3'',1'''-quaterphenyl]-2'-carboxamide (6j):



6j

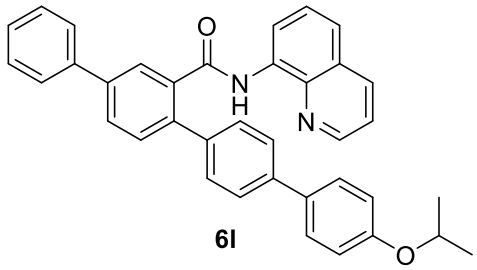
Following general procedure B, the compound **6j** was obtained after purification by column chromatography on silica gel (EtOAc:hexane = 20:80) as a yellow solid (94 mg, 96%, 0.2 mmol scale);R_f = 0.5 (EtOAc:hexane = 20:80); mp 185-187 ^oC; IR (DCM): 3329, 1680, 1511, 1265, 726 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ_H 9.75 (1H, s), 8.62-8.60 (1H, m), 8.54 (1H, dd, J_1 = 4.2 Hz, J_2 = 1.4 Hz), 8.06–8.04 (1H, m), 7.84 (1H, s), 7.61–7.59 (1H, m), 7.55–7.50 (5H, m), 7.43 - 7.27 (10H, m), 7.13 (2H, d, J = 7.9 Hz), 2.27 (3H, s); $^{13}C\{^1H\}$ NMR (~101 MHz, $CDCl_3$): δ_C 167.8, 147.9, 141.0, 140.9, 140.9, 140.7, 140.4, 138.3, 137.5, 137.1, 136.3, 136.0, 134.3, 129.6, 129.4, 129.1, 129.1, 128.7, 128.6, 128.5, 127.7, 127.7, 127.6, 127.2, 127.1, 126.1, 121.5, 121.4, 116.5, 21.2.; HRMS (ESI): *m/z* $[M+H]^+$ calcd for $C_{35}H_{27}N_2O$: 491.2123 found, 491.2101.

***N*-(Quinolin-8-yl)-[1,1':3',1'':3'',1'''-quaterphenyl]-2'-carboxamide (6k):** Following general procedure B, the compound **6k** was obtained after purification by column chromatography on silica gel (EtOAc:hexane = 20:80) as a colourless solid (82 mg, 86%, 0.2 mmol scale); R_f = 0.5 (EtOAc:hexane = 20:80); mp 131-133 °C; IR (DCM): 3343, 1676, 1521, 1261, 750 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ_H 9.78 (1H, s), 8.63 (1H, d, J = 6.6 Hz), 8.55 (1H, dd, J_1 = 4.2 Hz, J_2 = 1.5 Hz), 8.04 (1H, dd, J_1 = 8.3 Hz, J_2 = 1.5 Hz), 7.88 (1H, s), 7.65–7.62 (3H, m), 7.59–7.53 (3H, m), 7.47–7.40 (5H, m), 7.37–7.23 (8H, m); $^{13}C\{^1H\}$ NMR (~101 MHz, $CDCl_3$): δ_C 167.6, 147.9, 141.0, 140.8, 140.6, 140.4, 140.4, 138.2, 136.3, 135.9, 134.2, 129.6, 129.4, 129.3, 128.7, 128.5, 128.2, 127.7, 127.6, 127.5, 127.4, 127.1, 127.1, 126.1, 121.5, 121.3, 116.4; HRMS (ESI): *m/z* $[M+H]^+$ calcd for $C_{34}H_{25}N_2O$: 477.1967 found, 477.1947.



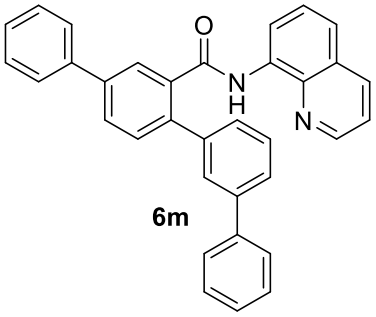
6k

4-Isopropoxy-*N*-(quinolin-8-yl)-[1,1':4',1'':4'',1'''-quaterphenyl]-2''-carboxamide (6l): Following general procedure B, the compound **6l** was obtained after purification by column chromatography on silica gel (EtOAc:hexane = 20:80) as a yellow solid (40 mg, 75%, 0.1 mmol scale); R_f = 0.4 (EtOAc:hexane = 20:80); mp: 194-196 °C; IR (DCM): 3334, 1674, 1512,1264, 726 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ_H 9.95 (1H, s), 8.89 (1H, dd, J_1 = 7.6 Hz, J_2 = 1.0 Hz), 8.49 (1H, dd, J_1 = 4.2 Hz, J_2 = 1.6 Hz), 8.22 (1H, d, J = 1.8 Hz), 8.07 (1H, dd, J_1 = 8.2 Hz, J_2 = 1.5 Hz), 7.84 (1H, dd, J_1 = 8.0 Hz, J_2 = 2.0 Hz), 7.77–7.75 (2H, m), 7.66–7.63 (3H, m), 7.59–7.48 (6H, m), 7.45–7.41 (1H, m), 7.35 (2H, d, J = 8.7 Hz), 7.33–7.28 (1H, m), 6.91 (2H, d, J = 8.7 Hz), 4.62-4.56 (1H, m), 1.38 (6H, d, J = 6.1 Hz); $^{13}C\{^1H\}$ NMR (~101 MHz, $CDCl_3$): δ_C 167.9, 157.5, 147.8, 140.5, 140.3, 139.9, 138.8, 138.5, 137.8, 136.4, 136.0, 134.6, 132.9, 131.2, 129.5, 129.1, 129.0, 128.1, 127.8, 127.7, 127.3, 127.2, 126.8, 121.7, 121.4, 116.4, 115.9, 69.9, 22.1; HRMS (ESI): *m/z* $[M+H]^+$ calcd for $C_{37}H_{31}N_2O_2$: 535.2386 found, 535.2386.



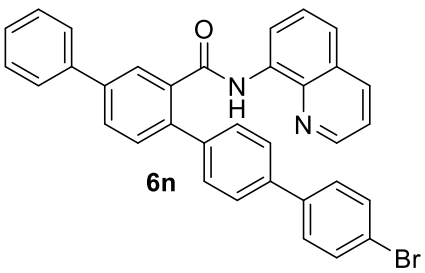
6l

***N*-(Quinolin-8-yl)-[1,1':3',1'':4'',1'''-quaterphenyl]-2''-carboxamide (6m):** Following general procedure B, the compound **6m** was obtained after purification by column chromatography on silica gel (EtOAc:hexane = 20:80) as a brown solid (71 mg, 74%, 0.2 mmol scale); R_f = 0.5 (EtOAc:hexane = 20:80); mp 130-132 °C; IR (DCM): 1670, 1527, 1479, 1329, 757 cm^{-1}; ^1H NMR (400 MHz, CCl_3): δ_H 9.92 (1H, s), 8.89 (1H, d, J = 7.6 Hz), 8.41 (1H, dd, J_1 = 4.2 Hz, J_2 = 1.4 Hz), 8.22 (1H, d, J = 1.2 Hz), 8.07 (1H, dd, J_1 = 8.2 Hz, J_2 = 1.5 Hz), 7.86–7.84 (2H, m), 7.75 (2H, d, J = 7.8 Hz), 7.66 (1H, d, J = 8.0 Hz),7.57–7.29 (14H, m);$^{13}C\{^1H\}$ NMR (~101 MHz, $CDCl_3$): δ_C 167.8, 147.9, 141.5, 140.9, 140.7, 140.1, 139.9, 138.9, 138.4, 136.7, 136.0, 134.5, 131.2, 129.1, 129.0, 128.9, 128.7, 128.0, 128.0, 127.9, 127.8, 127.7, 127.3, 127.3, 127.2, 127.2, 126.5, 121.7, 121.4, 116.3; HRMS (ESI): *m/z* $[M+H]^+$ calcd for $C_{34}H_{25}N_2O$: 477.1967 found, 477.1964.



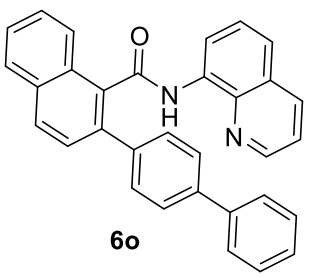
6m

Bromo-*N*-(quinolin-8-yl)-[1,1':4',1'':4'',1'''-quaterphenyl]-2''-carboxamide (6n): Following general procedure B, the compound **6n** was obtained after purification by column chromatography on silica gel (EtOAc:hexane = 20:80) as a brown solid (39 mg, 71%, 0.2 mmol scale); R_f = 0.5 (EtOAc:hexane = 20:80); mp 163-165 °C; IR (DCM): 3324, 1666, 1530, 1266, 736 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ_H 9.95 (1H, s), 8.87 (1H, d, J = 7.5 Hz), 8.49 (1H, dd, J_1 = 4.1, J_2 = 1.2 Hz), 8.20 (1H, d, J = 1.3 Hz), 8.10-8.08 (1H, m), 7.85 (1H, dd, J_1 = 8.0 Hz, J_2 = 1.7 Hz), 7.75 (2H, d, J = 7.4 Hz), 7.67–7.63 (3H, m), 7.59-7.49 (8H, m), 7.45–7.41 (1H, m), 7.32-7.27 (3H, m); $^{13}C\{^1H\}$ NMR (~101 MHz, $CDCl_3$): δ_C 167.8, 147.8, 140.8, 139.8, 139.5, 139.3, 139.0, 138.5, 138.5, 136.5, 136.0, 134.5, 131.8, 131.2, 129.6, 129.2, 129.0, 128.6, 128.0, 127.9, 127.8, 127.3, 127.2, 127.0, 121.7, 121.6, 121.4, 116.5; HRMS (ESI): *m/z* $[M+H]^+$ calcd for $C_{34}H_{24}BrN_2O$: 555.1072 found, 555.1070.



6n

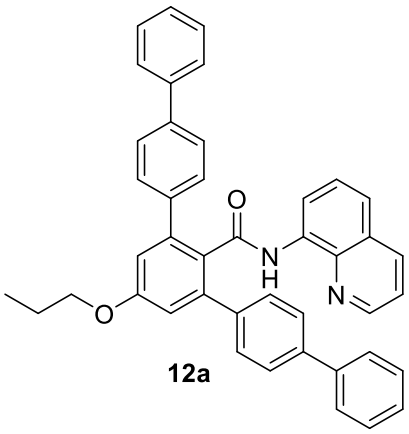
2-([1,1'-Biphenyl]-4-yl)-*N*-(quinoline-8-yl)-1-naphthamide (6o): Following general procedure B, the compound **6o** was obtained after purification by column chromatography on silica gel (EtOAc:hexane = 20:80) as a colourless solid (36 mg, 80%, 0.1 mmol scale); R_f = 0.4 (EtOAc:hexane = 20:80); mp: 211-213 °C; IR (DCM): 3337, 1672, 1522, 1328, 757 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ_H 9.93 (1H, s), 8.98 (1H, d, J = 7.6 Hz), 8.56 (1H, dd, J_1 = 4.1 Hz, J_2 = 1.1 Hz), 8.29 (1H, d, J = 7.6 Hz), 8.09–



6o

8.05 (2H, m), 7.99- 7.97 (1H, m), 7.77 (2H, d, J = 7.8 Hz), 7.70 (1H, d, J = 8.5 Hz), 7.62– 7.50 (6H, m), 7.44 (2H, d, J = 7.2 Hz), 7.40–7.36 (3H, m), 7.34–7.28 (1H, m); $^{13}C\{^{1}H\}$ NMR (~101 MHz, $CDCl_3$): δ_C 168.0, 148.0, 140.4, 140.2, 139.2, 138.4, 136.5, 136.0, 134.5, 133.7, 132.6, 130.6, 129.8, 129.4, 128.6, 128.1, 127.8, 127.7, 127.5, 127.2, 127.2, 127.1, 126.9, 126.5, 125.6, 121.9, 121.4, 116.7; HRMS (ESI): *m/z* $[M+H]^+$ calcd for $C_{32}H_{23}N_2O$: 451.1810 found, 451. 1808.

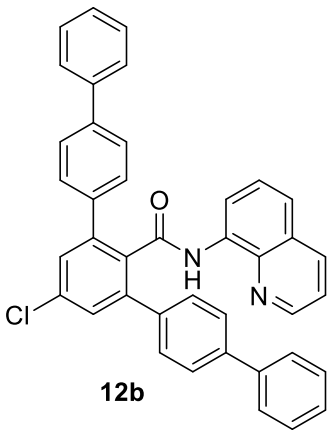
5''-Propoxy-*N*-(quinoline-8-yl)-[1,1':4',1'':3'',1''':4''',1'''':quinquephenyl]-2''-carboxamide (12a): Following general procedure B, the compound **12a** was obtained after



12a

purification by column chromatography on silica gel (EtOAc:hexane = 20:80) as a brown coloured solid (92 mg, 76%, 0.2 mmol scale); R_f = 0.4 (EtOAc:hexane = 20:80); mp 210-212 ^{o}C; IR (DCM): 3343, 1673, 1521, 1479, 1261 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 9.69 (1H, s), 8.58–8.55 (2H, m), 8.02 (1H, dd, J_1 = 8.3 Hz, J_2 = 1.6 Hz), 7.66 (4H, d, J = 8.2 Hz), 7.51 (4H, d, J = 8.2 Hz), 7.47–7.45 (5H, m), 7.42–7.37 (5H, m), 7.33–7.27 (3H, m), 7.08 (2H, s), 4.11 (2H, t, J = 6.5 Hz), 1.95–1.89 (2H, m), 1.12 (3H, t, J = 7.4 Hz); $^{13}C\{^{1}H\}$ NMR (~101 MHz, $CDCl_3$): δ_C 167.7, 159.4, 147.7, 142.1, 140.7, 140.2, 139.6, 138.3, 135.9, 134.5, 129.0, 129.0, 128.6, 127.6, 127.2, 127.2, 127.0, 127.0, 121.4, 121.3, 116.4, 115.4, 69.9, 22.6, 10.6; HRMS (ESI): *m/z* $[M+H]^+$ calcd for $C_{43}H_{35}N_2O_2$: 611.2699 found, 611.2674.

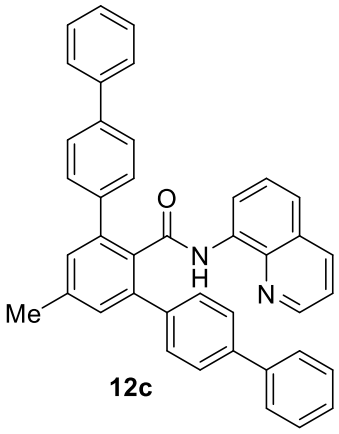
5''-Chloro-*N*-(quinoline-8-yl)-[1,1':4',1'':3'',1''':4''',1'''':quinquephenyl]-2''-carboxamide (12b): Following general procedure B, the compound **12b** was obtained after



12b

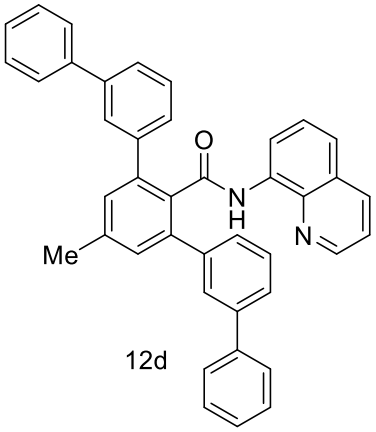
purification by column chromatography on silica gel (EtOAc:hexane = 20:80) as a colourless solid (52 mg, 45%, 0.2 mmol scale); R_f = 0.4 (EtOAc:hexane = 20:80); mp 192-194 ^{o}C; IR (DCM): 3335, 1679, 1524, 1269, 753 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 9.72 (1H, s), 8.56–8.54 (2H, m), 8.04 (1H, dd, J_1 = 8.3 Hz, J_2 = 1.6 Hz), 7.65 (4H, d, J = 8.2 Hz), 7.56–7.51 (6H, m), 7.47–7.43 (6H, m), 7.42–7.37 (4H, m), 7.34–7.30 (3H, m); $^{13}C\{^{1}H\}$ NMR (~101 MHz, $CDCl_3$): δ_C 166.7, 147.9, 142.1, 140.7, 140.4, 138.3, 138.1, 136.0, 135.1, 134.5, 134.1, 129.2, 129.0, 128.7, 127.7, 127.4, 127.2, 127.1, 127.0, 121.8, 121.4, 116.6; HRMS (ESI): *m/z* $[M+H]^+$ calcd for $C_{40}H_{28}ClN_2O$: 587.1890 found, 587.1872.

5''-Methyl-*N*-(quinoline-8-yl)-[1,1':4',1'':3'',1''':4''',1'''':quinquephenyl]-2''-carboxamide (12c): Following general procedure B, the compound **12c** was obtained after purification by column chromatography on silica gel (EtOAc:hexane = 20:80) as a colourless solid (81 mg, 72%, 0.2 mmol scale); R_f = 0.4 (EtOAc:hexane = 20:80); mp 126-128 °C; IR (DCM): 3342, 3047, 1681, 1511, 1483, 755 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 9.71 (1H, s), 8.59 -8.56 (2H, m), 8.03 (1H, dd, J_1 = 8.3 Hz, J_2 = 1.6 Hz), 7.66–7.64 (4H, m), 7.52-7.49 (3H, m), 7.47-7.45 (4H, m), 7.42–7.37 (8H, m), 7.33–7.28 (4H, m), 2.55 (3H, s); $^{13}C\{^1H\}$ NMR (~101 MHz, $CDCl_3$): δ 167.9, 147.8, 140.7, 140.3, 140.1, 139.6, 139.4, 138.4, 136.0, 134.4, 133.5, 130.2, 129.1, 128.6, 127.7, 127.2, 127.0, 127.0, 127.0, 121.5, 121.3, 116.5, 21.5; HRMS (ESI): *m/z* $[M+H]^+$ calcd for $C_{41}H_{31}N_2O$: 567.2436 found, 567.2442.



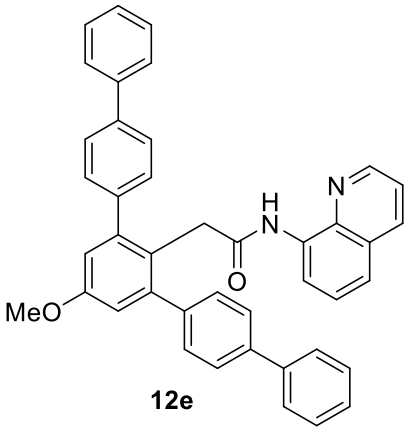
12c

5''-Methyl-*N*-(quinoline-8-yl)-[1,1':3',1'':3'',1''':3''',1'''':quinquephenyl]-2''-carboxamide (12d): Following general procedure B, the compound **12d** was obtained after purification by column chromatography on silica gel (EtOAc:hexane = 20:80) as a colourless solid (83 mg, 74%, 0.2 mmol scale); R_f = 0.4 (EtOAc:hexane = 20:80); mp 182-184 °C; IR (DCM): 3069, 1691, 1505, 1267 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ_H 10.00 (1H, s), 8.66–8.65 (1H, m), 8.34–8.31 (2H, m), 7.81 (2H, s), 7.60 (1H, dd, J_1 = 8.3 Hz, J_2 = 1.0 Hz), 7.54–7.39 (14H, m), 7.27–7.24 (6H, m), 2.51 (3H, s); $^{13}C\{^1H\}$ NMR (~101 MHz, $CDCl_3$): δ_C 167.9, 147.9, 141.0, 140.9, 140.9, 140.5, 139.4, 138.2, 135.9, 134.3, 133.8, 130.2, 128.7, 128.5, 127.7, 127.6, 127.6, 127.2, 127.1, 126.1, 121.5, 121.3, 116.4, 21.4; HRMS (ESI): *m/z* $[M+H]^+$ calcd for $C_{41}H_{31}N_2O$: 567.2436 found, 567.2441.



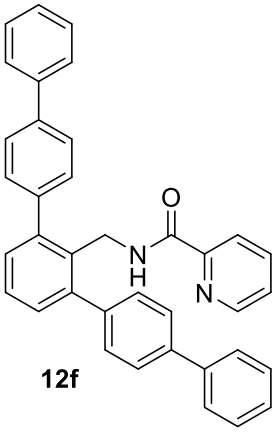
12d

2-(5’’-Methoxy-[1,1’:4’,1’’:3’’,1’’’:4’’’,1’’’’-quinquephenyl]-2’’-yl)-*N*-(quinoline-8-yl)acetamide (12e): Following general procedure B, the compound **12e** was obtained after purification by column chromatography on silica gel (EtOAc:hexane = 20:80) as a yellow coloured solid (108 mg, 91%, 0.2 mmol scale); R_f = 0.4 (EtOAc:hexane = 20:80); mp 188-190 ^oC; IR (DCM): 3341, 3049, 1682, 1515, 1265 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ_H 9.43 (1H, s), 8.62 (1H, d, J = 5.6 Hz), 8.59 (1H, dd, J_1 = 4.4 Hz, J_2 = 1.6 Hz), 8.17 (1H, dd, J_1 = 8.2 Hz, J_2 = 1.1 Hz), 7.61–7.57 (8H, m), 7.55–7.48 (6H, m), 7.43–7.39 (4H, m), 7.37 – 7.32 (3H, m), 7.03 (2H, s), 3.93 (3H, s), 3.89 (2H, s); $^{13}C\{^1H\}$ NMR (~101 MHz, $CDCl_3$): δ_C 170.8, 158.0, 147.4, 144.7, 140.6, 140.5, 140.0, 137.2, 133.8, 129.6, 128.7, 128.0, 127.7, 127.2, 126.9, 123.0, 121.7, 121.4, 117.5, 115.2, 55.5, 39.6; HRMS (ESI): *m/z* $[M+H]^+$ calcd for $C_{42}H_{33}N_2O_2$: 597.2542 found, 597.2541.



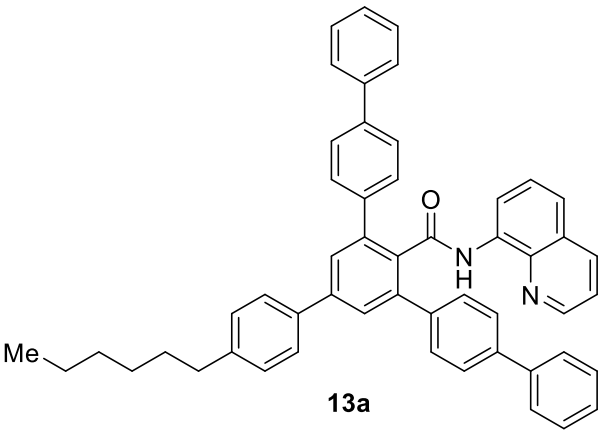
12e

***N*-([1,1’:4’,1’’:3’’,1’’’:4’’’,1’’’’-Quinquephenyl]-2’’-ylmethyl)picolinamide (12f):** Following the general procedure B, **12f** was obtained after purification by column chromatography on silica gel (EtOAc:Hexane = 20:80) as a colourless solid (42 mg, 41%, 0.2 mmol scale); R_f = 0.6 (EtOAc:Hexane = 20:80); mp: 187-189 ^oC; IR (DCM): 3398, 3036, 1678, 1514, 760 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ_H 8.44–8.43 (1H, m), 7.98 (1H, d, J = 7.8 Hz), 7.89 (1H, br. S), 7.73 (1H, td, J_1 = 7.7 Hz, J_2 = 1.7 Hz), 7.62–7.60 (8H, m), 7.52–7.44 (9H, m), 7.41–7.35 (5H, m), 4.66 (2H, d, J = 5.0 Hz); $^{13}C\{^1H\}$ NMR (~101 MHz, $CDCl_3$): δ_C 163.0, 149.7, 147.8, 143.4, 140.8, 140.2, 140.1, 137.1, 132.8, 129.9, 129.5, 128.7, 127.5, 127.3, 127.1, 127.0, 125.8, 121.9, 39.6; HRMS (ESI): *m/z* $[M+H]^+$ calcd for $C_{37}H_{29}N_2O$: 517.2280 found, 517.2268.



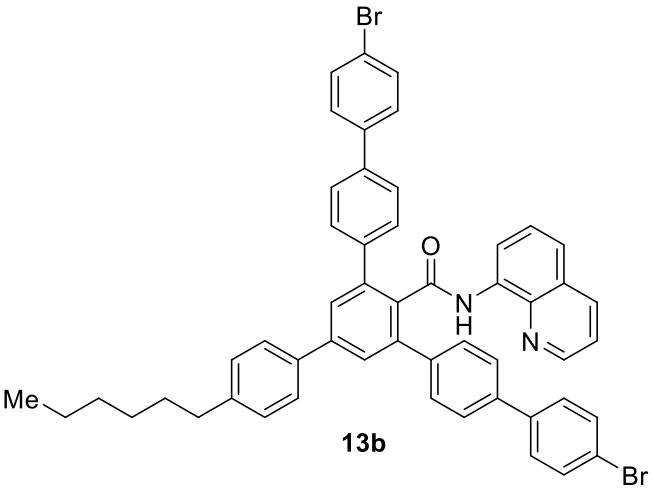
12f

5’’-(4-Hexylphenyl)-*N*-(quinoline-8-yl)-[1,1’:4’,1’’:3’’,1’’’:4’’’,1’’’’-quinquephenyl]-2’’-carboxamide (13a): Following the general procedure B, **13a** was obtained after purification by column chromatography on silica gel (EtOAc:Hexane = 20:80) as a brown solid (114 mg, 80%, 0.2 mmol scale); R_f = 0.5 (EtOAc:Hexane = 20:80); mp: 165-167 ^oC; IR (DCM): 3343, 1680, 1511, 1262, 747 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ_H 9.78 (1H, s), 8.61-8.57 (2H, m), 8.03 (1H, dd, J_1 = 8.2 Hz, J_2 = 1.2 Hz), 7.78 (2H, s), 7.72-7.66 (6H, m), 7.53 (4H, d, J = 8.2 Hz), 7.48-7.42 (6H, m), 7.41-7.37 (4H, m), 7.35-7.29 (5H, m), 2.71 (2H, t, J = 7.6 Hz), 1.73–1.66 (2H, m), 1.45–1.28 (6H, m), 0.93 (3H, t, J = 7.0 Hz); $^{13}C\{^1H\}$ NMR (~101 MHz, $CDCl_3$): δ_C 167.8, 147.9, 143.1, 142.4, 140.9, 140.7, 140.3, 139.6, 138.4, 137.4, 136.0, 134.7, 134.4, 129.3, 129.2, 128.7, 128.2, 127.7, 127.3, 127.2, 127.1, 127.1, 121.7, 121.5, 116.7, 35.8, 31.9, 31.6, 29.2, 22.8, 14.3; HRMS (ESI): *m/z* $[M+H]^+$ calcd for $C_{52}H_{45}N_2O$: 713.3532 found, 713.3512.



13a

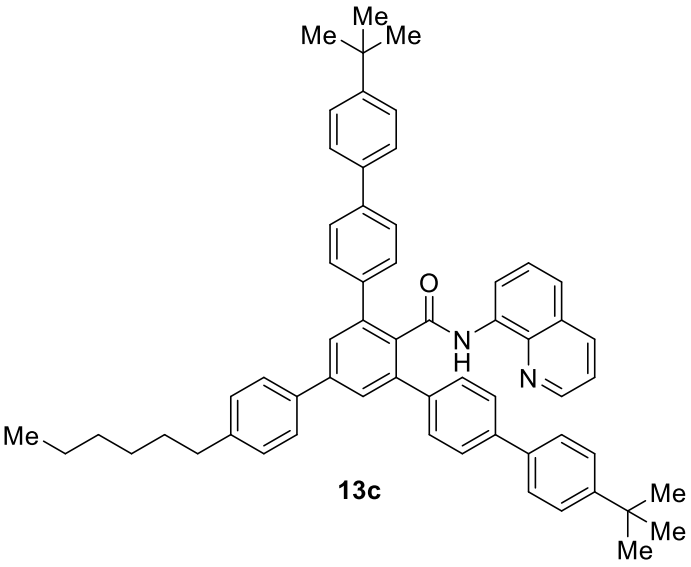
4,4’’’’-Dibromo-5’’-(4-hexylphenyl)-*N*-(quinolin-8-yl)-[1,1’:4’,1’’:3’’,1’’’:4’’’,1’’’’-quinquephenyl]-2’’-carboxamide (13b): Following general procedure B, the compound **13b** was obtained after purification by column chromatography on silica gel (EtOAc:hexane = 20:80) as a yellow solid (100 mg, 77%, 0.15 mmol scale); R_f = 0.6 (EtOAc:hexane = 20:80); mp 185-187 ^oC; IR (DCM): 3328, 1678, 1520, 1483, 815 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ_H 9.77 (1H, s), 8.59 (1H, dd, J_1 = 6.9 Hz, J_2 = 4.9 Hz), 8.57–8.56 (1H, m), 8.04 (1H, dd, J_1 = 8.3 Hz, J_2 = 1.5 Hz), 7.77 (2H, s), 7.71 (4H, d, J = 8.2 Hz), 7.67 (2H, d, J = 8.1 Hz), 7.52–7.43 (10H, m), 7.35–7.30 (7H, m), 2.71 (2H, t, J = 7.8 Hz), 1.72–1.68 (2H, m), 1.43–1.29 (6H, m), 0.93 (3H, t, J = 6.8 Hz); $^{13}C\{^1H\}$ NMR (~101 MHz, $CDCl_3$): δ_C 167.6, 147.8, 143.1, 142.5, 140.7, 139.9, 139.5, 139.0, 138.3, 137.3, 136.0, 134.5, 134.3, 131.8, 129.3, 129.1, 128.6, 128.1, 127.7, 127.2, 127.2, 126.9, 121.7, 121.5, 121.4, 116.6, 35.7, 31.8, 31.5,



13b

29.1, 22.7, 14.2; HRMS (ESI): *m/z* $[M+H]^+$ calcd for $C_{52}H_{43}Br_2N_2O$: 869.1742 found, 869.1700.

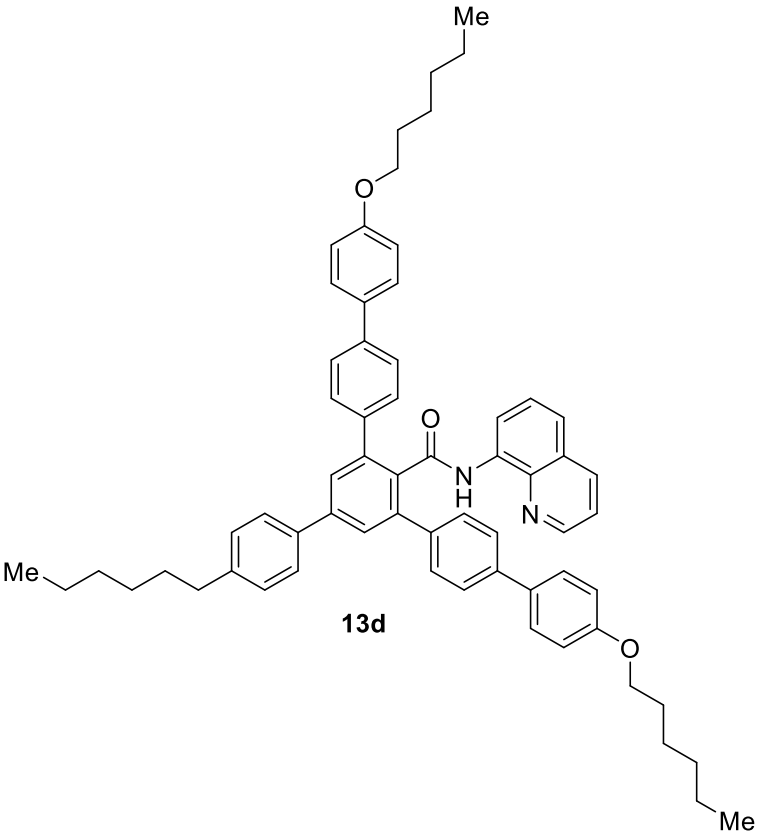
4,4''''-Di-*tert*-butyl-5''-(4-hexylphenyl)-*N*-(quinolin-8-yl)-[1,1':4',1'':3'',1''':4''',1''''-quinquephenyl]-2''-carboxamide (13c): Following general procedure B, the compound **13c**



13c

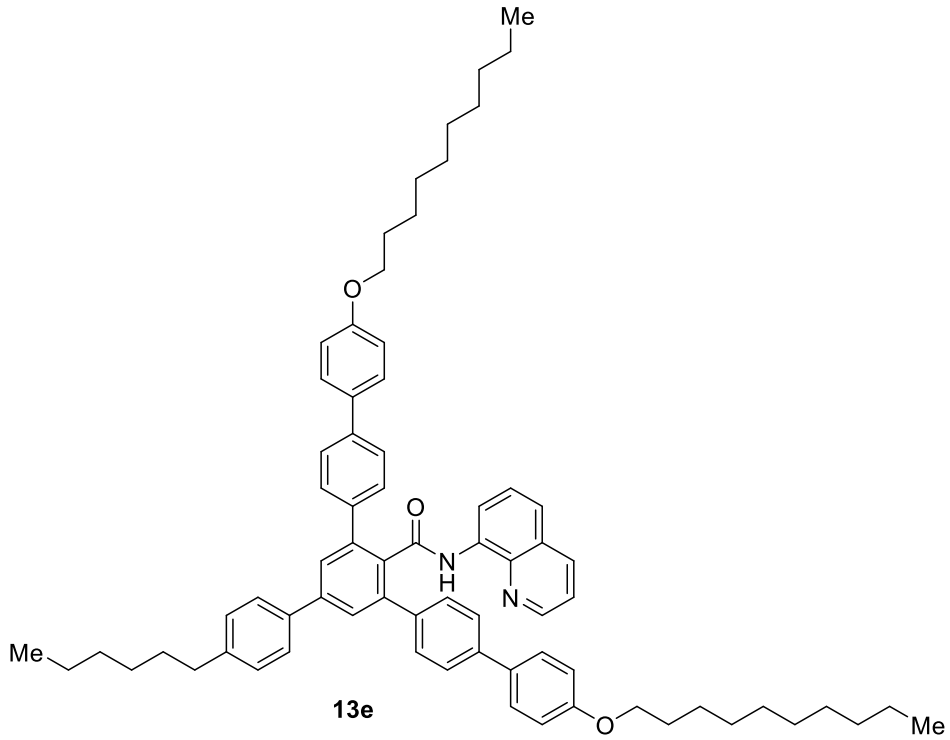
was obtained after purification by column chromatography on silica gel (EtOAc:hexane = 20:80) as a brown coloured solid (76 mg, 62%, 0.15 mmol scale); R_f = 0.6 (EtOAc:hexane = 20:80); mp 174-176 ^oC; IR (DCM): 3333, 1679, 1512, 1331, 1265 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ_H 9.80 (1H, s), 8.62–8.59 (2H, m), 8.05 (1H, dd, J_1 = 8.3 Hz, J_2 = 1.6 Hz), 7.79 (2H, s), 7.73 -7.68 (6H, m), 7.56–7.54 (4H, m), 7.48–7.42 (10H, m), 7.36–7.31 (3H, m), 2.72 (2H, t, J = 7.6 Hz), 1.73–1.70 (2H, m), 1.46–1.33 (6H, m), 1.37 (18H, s), 0.95 (3H, t, J = 6.9 Hz); $^{13}C\{^1H\}$ NMR (~101 MHz, $CDCl_3$): δ_C 167.7, 150.2, 147.8, 143.0, 142.3, 140.9, 140.1, 139.2, 138.4, 137.8, 137.4, 136.0, 134.6, 134.3, 129.1, 129.1, 128.0, 127.7, 127.2, 126.9, 126.7, 125.6, 121.6, 121.4, 116.6, 35.7, 34.5, 31.8, 31.5, 31.4, 29.1, 22.7, 14.2; HRMS (ESI): *m/z* $[M+H]^+$ calcd for $C_{60}H_{61}N_2O$: 825.4787 found, 825.4783.

4,4''''-Bis(hexyloxy)-5''-(4-hexylphenyl)-*N*-(quinolin-8-yl)-[1,1':4',1'':3'',1''':4''',1''''-quinquephenyl]-2''-carboxamide (13d): Following general procedure B, the compound **13d** was obtained after purification by column chromatography on silica gel (EtOAc:hexane = 20:80) as a colourless solid (95 mg, 70%, 0.15 mmol scale); R_f = 0.4 (EtOAc:hexane = 20:80); mp: 103-105 ^{o}C; IR (DCM): 3338, 1680, 1506, 1255, 732 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 9.82 (1H, s), 8.65 (1H, d, J = 7.3 Hz), 8.59 (1H, d, J = 4.0 Hz), 8.03 (1H, d, J = 8.2 Hz), 7.80 (2H, s), 7.73–7.69 (6H, m), 7.52–7.41 (10H, m), 7.36 (2H, d, J = 7.8 Hz), 7.32–7.28 (1H, m), 6.94 (4H, d, J = 8.4 Hz), 4.01 (4H, t, J = 6.5 Hz), 2.73 (2H, t, J = 7.6 Hz), 1.87–1.80 (4H, m), 1.76–1.69 (2H, m), 1.53–1.32 (18H, m), 0.96 (9H, t, J = 6.5 Hz); ^{13}C{^{1}H } NMR (~101 MHz, $CDCl_3$): δ_C 167.8, 158.7, 147.9, 143.0, 142.3, 141.0, 139.9, 138.8, 138.4, 137.4, 136.0, 134.6, 134.4, 133.0, 129.2, 129.1, 128.0, 127.7, 127.2, 126.6, 121.6, 121.4, 116.6, 114.7, 68.1, 35.7, 31.8, 31.7, 31.5, 29.3, 29.1, 25.8, 22.7, 22.7, 14.2, 14.1; HRMS (ESI): *m/z* $[M+H]^+$ calcd for $C_{64}H_{69}N_2O_3$: 913.5308 found, 913.5303.



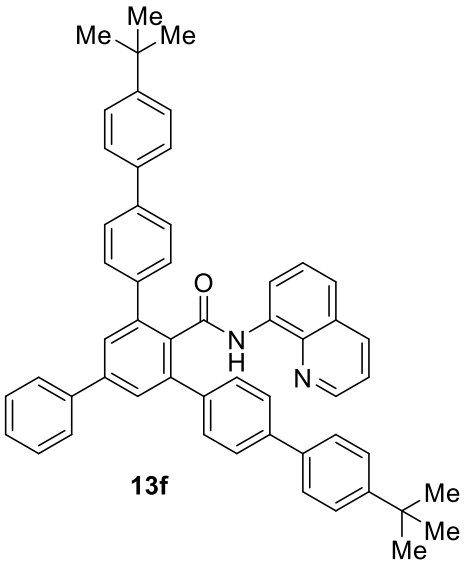
13d

4,4''''-Bis(decyloxy)-5''-(4-hexylphenyl)-*N*-(quinolin-8-yl)-[1,1':4',1'':3'',1''':4''',1''''-quinquephenyl]-2''-carboxamide (13e): Following general procedure B, the compound **13e** was obtained after purification by column chromatography on silica gel (EtOAc:hexane = 20:80) as a semi-solid (57 mg, 56%, 0.1 mmol scale); R_f = 0.6 (EtOAc:hexane = 20:80); IR (DCM): 3330, 1678, 1508, 1320, 726 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ_H δ 9.78 (1H, s), 8.62 (1H, dd, J_1 = 7.2 Hz, J_2 = 1.5 Hz), 8.58 (1H, dd, J_1 =4.2 Hz, J_2 = 1.5 Hz), 8.04 (1H, dd, J_1 = 8.3 Hz, J_2 = 1.4 Hz), 7.77 (2H, s), 7.70–7.67 (7H, m), 7.50–7.39 (9H, m), 7.35–7.29 (3H, m), 6.92 (4H, d, J = 8.8 Hz), 3.99 (4H, t, J = 6.6 Hz), 2.71 (2H, t, J = 7.8 Hz), 1.85–1.78 (4H, m), 1.73–1.69 (2H, m), 1.52–1.31 (34H, m), 0.96–0.90 (9H, m). $^{13}C\{^1H\}$ NMR (~101 MHz, $CDCl_3$): δ_C 167.8, 158.7, 147.8, 143.0, 142.3, 140.9, 139.9, 138.8, 138.4, 137.4, 135.9, 134.6, 134.4, 133.0, 129.1, 129.1, 128.0, 127.7, 127.2, 126.6, 121.6, 121.4, 116.6, 114.7, 68.1, 35.7, 31.9, 31.9, 31.8, 31.5, 29.6, 29.5, 29.4, 29.4, 29.3, 29.1, 26.1, 22.7, 22.7, 14.1; HRMS (ESI): *m/z* $[M+H]^+$ calcd for $C_{72}H_{84}N_2O_3$: 1025.6560 found, 1025.6573.



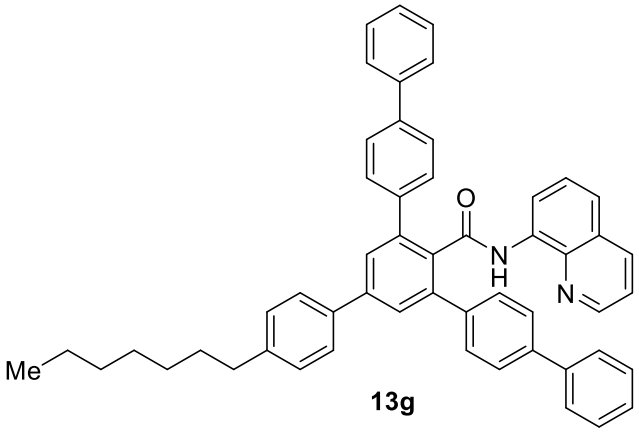
13e

4,4''''-Di-*tert*-butyl-5''-phenyl-*N*-(quinolin-8-yl)-[1,1':4',1'':3'',1''':4''',1''''-quinquephenyl]-2''-carboxamide (13f): Following general procedure B, the compound **13f** was obtained after purification by column chromatography on silica gel (EtOAc:hexane = 20:80) as a yellow solid (136 mg, 92%, 0.2 mmol scale); R_f = 0.5 (EtOAc:hexane = 20:80); mp 177-179 ^oC; IR (DCM): 3338, 2958, 1677, 1505, 1263, 742 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ_H 9.89 (1H, J = 3.6 Hz), 8.68-8.67 (1H, m), 8.63–8.62 (1H, m), 8.05 (1H, dd, J_1 = 8.3 Hz, J_2 = 1.6 Hz), 7.86–7.77 (8H, m), 7.62–7.55 (6H, m), 7.52–7.45 (11H, m), 7.33 (1H, dd, J_1 = 8.3 Hz, J_2 = 4.2 Hz); 1.42 (18H, s); $^{13}C\{^1H\}$ NMR (~101 MHz, $CDCl_3$): δ_C 167.6, 150.2, 147.8, 142.3, 140.9, 140.1, 139.1, 138.3, 137.7, 136.0, 134.9, 134.3, 129.1, 129.0, 128.2, 128.0, 127.7, 127.4, 127.2, 126.9, 126.7, 125.6, 121.6, 121.4, 116.5, 34.5, 31.3; HRMS (ESI): *m/z* $[M+H]^+$ calcd for $C_{54}H_{49}N_2O$: 741.3845 found, 741.3849.



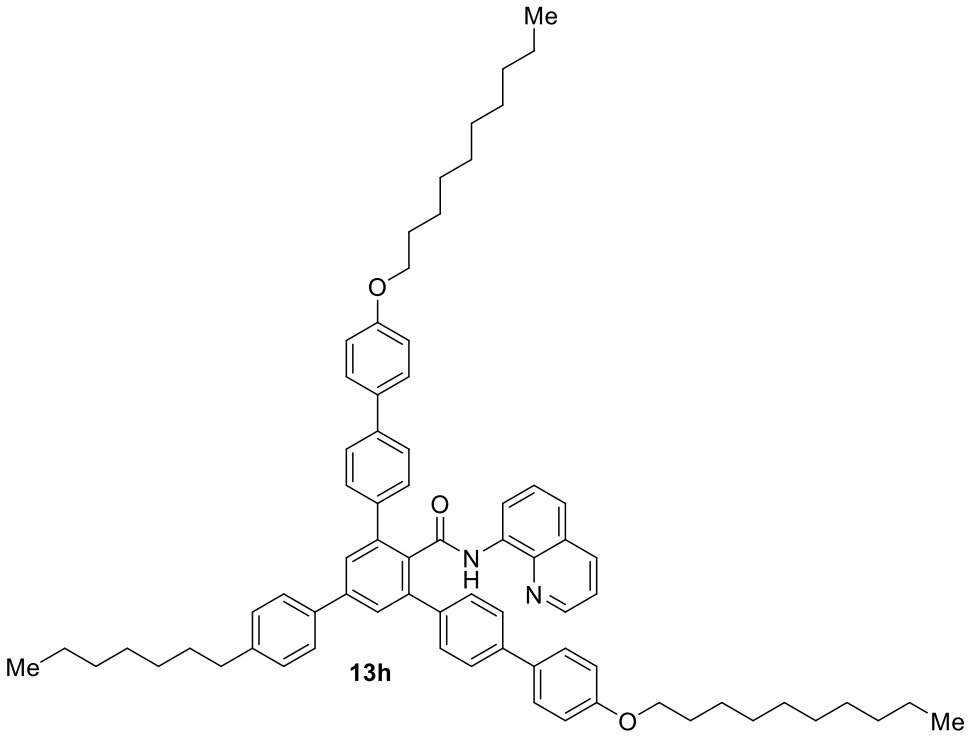
13f

5''-(4-Heptylphenyl)-*N*-(quinolin-8-yl)-[1,1':4',1'':3'',1''':4''',1''''-quinquephenyl]-2''-carboxamide (13g): Following general procedure B, the compound **13g** was obtained after purification by column chromatography on silica gel (EtOAc:hexane = 20:80) as a semi-solid (108 mg, 75%, 0.2 mmol scale); R_f = 0.5 (EtOAc:hexane = 20:80); IR (DCM): 3335, 1676, 1510, 1264, 724 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ_H 9.79 (1H, s), 8.59–8.57 (2H, m), 8.04 (1H, dd, J_1 = 8.3 Hz, J_2 = 1.5 Hz), 7.78 (2H, s), 7.72 (4H, d, J = 8.2 Hz), 7.68 (2H, d, J = 8.0 Hz), 7.53 (4H, d, J = 8.2 Hz), 7.48-7.41 (6H, m), 7.42–7.37 (4H, m), 7.35-7.30 (5H, m), 2.71 (2H, t, J = 7.8 Hz), 1.71–1.68 (2H, m), 1.40–1.31 (8H, m), 0.94-0.91 (3H, m); $^{13}C\{^1H\}$ NMR (~101 MHz, $CDCl_3$): δ_C 167.7, 147.9, 143.1, 142.4, 140.9, 140.7, 140.2, 139.5, 138.4, 137.4, 136.0, 134.6, 134.4, 129.2, 129.1, 128.7, 128.1, 127.7, 127.2, 127.1, 127.1, 121.6, 121.4, 116.6, 35.7, 31.9, 31.6, 29.4, 29.3, 22.7, 14.; HRMS (ESI): *m/z* $[M+H]^+$ calcd for $C_{53}H_{47}N_2O$: 727.3688 found, 727.3690.

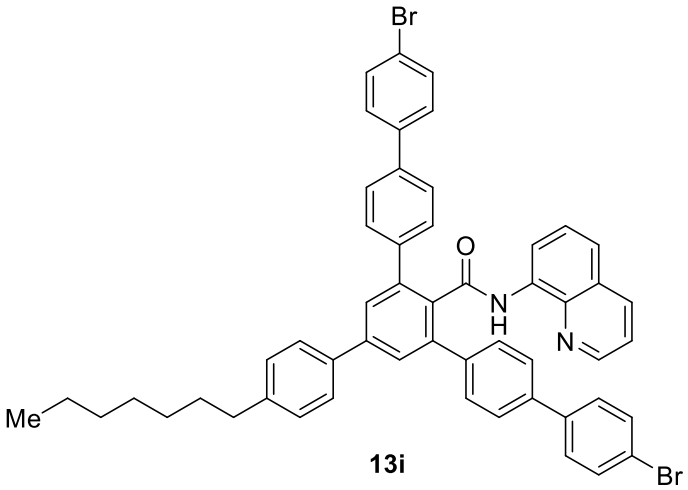


13g

4,4''''-Bis(decyloxy)-5''-(4-heptylphenyl)-*N*-(quinolin-8-yl)-[1,1':4',1'':3'',1''':4''',1''''-quinquephenyl]-2''-carboxamide (13h): Following general procedure B, the compound **13h** was obtained after purification by column chromatography on silica gel (EtOAc:hexane = 20:80) as a semi-solid (60 mg, 58%, 0.1 mmol scale); R_f = 0.4 (EtOAc:hexane = 20:80); IR (DCM): 3330, 1676, 1505, 1262, 726 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ_H 9.77 (1H, s), 8.60 (1H, dd, J_1 = 7.0 Hz, J_2 = 1.8 Hz), 8.57 (1H, dd, J_1 = 4.2 Hz, J_2 = 1.6 Hz), 8.04 (1H, dd, J_1 = 8.3 Hz, J_2 = 1.6 Hz), 7.76 (2H, s), 7.69–7.66 (6H, m), 7.49–7.38 (10H, m), 7.34–7.29 (3H, m), 6.92 (4H, d, J = 8.8 Hz), 3.98 (4H, t, J = 6.6 Hz), 2.70 (2H, t, J = 7.9 Hz), 1.84–1.77 (4H, m), 1.72-1.68 (2H, m), 1.50–1.30 (36H, m), 0.94–0.89 (9H, m); $^{13}C\{^1H\}$ NMR (~101 MHz, $CDCl_3$): δ_C 167.8, 158.7, 147.8, 143.0, 142.3, 140.9, 139.9, 138.8, 138.4, 137.4, 135.9, 134.5, 134.4, 132.9, 129.1, 129.1, 128.0, 127.7, 127.2, 127.2, 126.6, 121.6, 121.4, 116.6, 114.6, 68.1, 35.7, 31.9, 31.9, 31.5, 29.6, 29.6, 29.4, 29.4, 29.4, 29.3, 29.2, 26.1, 22.7, 14.2; HRMS (ESI): *m/z* $[M+H]^+$ calcd for $C_{73}H_{87}N_2O_3$: 1039.6717 found, 1039.6710.

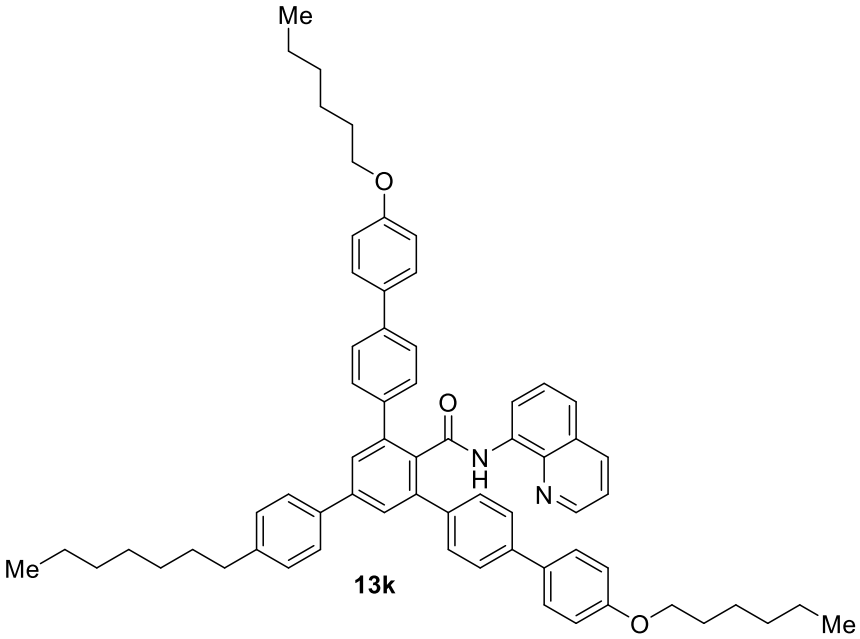


4,4''''-Dibromo-5''-(4-heptylphenyl)-*N*-(quinolin-8-yl)-[1,1':4',1'':3'',1''':4''',1''''-quinquephenyl]-2''-carboxamide (13i): Following general procedure B, the compound **13i** was obtained after purification by column chromatography on silica gel (EtOAc:hexane = 20:80) as a colourless solid (58 mg, 66%, 0.1 mmol scale); R_f = 0.5 (EtOAc:hexane = 20:80); mp: 163-165 ^{o}C; IR (DCM): 3339, 1676, 1520, 1263, 737 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 9.77 (1H, s), 8.60 (1H, dd, J_1 = 6.8 Hz, J_2 = 2.2 Hz), 8.57 (1H, dd, J_1 = 4.2 Hz, J_2 = 1.6 Hz), 8.05 (1H, dd, J_1 = 8.3 Hz, J_2 = 1.6 Hz), 7.77 (2H, s), 7.72–7.65 (6H, m), 7.52–7.43 (10H, m), 7.35–7.30 (7H, m), 2.71 (2H, t, J = 7.9 Hz), 1.72–1.68 (2H, m), 1.40–1.29 (8H, m), 0.92 (3H, t, J = 6.9 Hz); ^{13}C{^{1}H } NMR (~101 MHz, $CDCl_3$): δ_C 167.6, 147.8, 143.1, 142.5, 140.7, 139.9, 139.5, 139.0, 138.3, 137.2, 136.0, 134.5, 134.3, 131.7, 129.3, 129.1, 128.6, 128.1, 127.7, 127.2, 127.2, 126.9, 121.7, 121.5, 121.4, 116.6, 36.7, 31.9, 31.5, 29.4, 29.2, 22.7, 14.1; HRMS (ESI): *m/z* $[M+H]^+$ calcd for $C_{53}H_{45}BrN_2O$: 883.1899 found, 883.1896.



13i

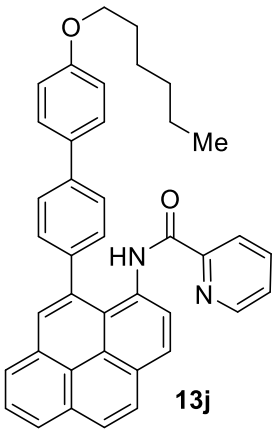
5''-(4-Heptylphenyl)-4,4''''-bis(hexyloxy)-*N*-(quinolin-8-yl)-[1,1':4',1'':3'',1''':4''',1''''-quinquephenyl]-2''-carboxamide (13k): Following general procedure B, the compound **13k** was obtained after purification by column chromatography on silica gel (EtOAc:hexane = 20:80) as a semi-solid (71 mg, 76%, 0.1 mmol scale); R_f = 0.4 (EtOAc:hexane = 20:80); IR (DCM): 3343, 1677, 1511, 1247, 820 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 9.80 (1H, s), 8.63 (1H, d, J = 7.2 Hz), 8.58 (1H, dd, J_1 = 4.2 Hz, J_2 = 1.6 Hz), 8.03 (1H, dd, J_1 = 8.3



13k

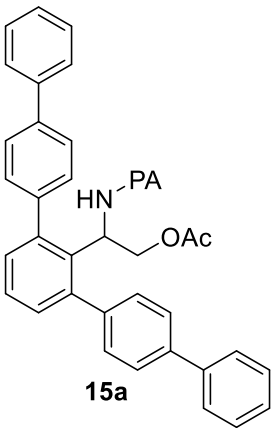
Hz, J_2 = 1.6 Hz), 7.78 (2H, s), 7.71–7.68 (6H, m), 7.50 (4H, d, J = 8.2 Hz), 7.47–7.40 (6H, m), 7.35 (2H, d, J = 8.1 Hz), 7.31 (1H, dd, J_1 = 8.3 Hz, J_2 = 4.2 Hz), 6.93 (4H, d, J = 8.8 Hz), 4.00 (4H, t, J = 6.6 Hz), 2.72 (2H, t, J = 7.6 Hz), 1.86–1.79 (4H, m), 1.73–1.70 (2H, m), 1.52–1.47 (4H, m), 1.40–1.31 (16H, m), 0.97–0.92 (9H, m); $^{13}C\{^1H\}$ NMR (~101 MHz, $CDCl_3$): δ_C 167.8, 158.7, 147.8, 143.0, 142.3, 140.9, 139.9, 138.8, 138.4, 137.4, 136.0, 134.6, 134.4, 133.0, 129.1, 129.1, 128.0, 127.7, 127.2, 126.6, 121.6, 121.4, 116.6, 114.7, 68.1, 35.7, 31.9, 31.6, 31.6, 29.4, 29.3, 29.3, 25.8, 22.7, 22.7, 14.2, 14.1; HRMS (ESI): *m/z* $[M+H]^+$ calcd for $C_{65}H_{71}N_2O_3$: 927.5465 found, 927.5493.

***N*-(10-(4'-(Hexyloxy)-[1,1'-biphenyl]-4-yl)pyren-1-yl)picolinamide (13j):** Following general procedure B, the compound **13j** was obtained after purification by column chromatography on silica gel (EtOAc:hexane = 20:80) as a brown solid (49 mg, 43%, 0.2 mmol scale); R_f = 0.4 (EtOAc:hexane = 20:80); mp: 165-167 °C; IR (DCM): 3379, 1683, 1516, 1247, 823 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ_H 10.00 (1H, s), 8.78 (1H, d, J = 8.4 Hz), 8.33 (1H, d, J = 8.4 Hz), 8.23 (1H, d, J = 7.4 Hz), 8.19–8.14 (3H, m), 8.11–8.09 (2H, m), 8.04 (1H, t, J = 7.6 Hz), 8.00 (1H, s), 7.74 (1H, td, J_1 = 7.6 Hz, J_2 = 1.6 Hz), 7.63 (2H, d, J = 8.2 Hz), 7.47 (2H, d, J = 8.2 Hz), 7.30–7.27 (2H, m), 7.15–7.12 (1H, m), 6.97–6.94 (2H, m), 4.03 (2H, t, J = 6.6 Hz), 1.87–1.82 (2H, m), 1.55–1.51 (2H, m), 1.42–1.38 (4H, m), 0.98 (3H, t, J = 7.0 Hz); $^{13}C\{^1H\}$ NMR (~101 MHz, $CDCl_3$): δ_C 162.1, 158.7, 149.7, 147.6, 141.2, 139.6, 136.9, 136.4, 132.8, 131.7, 131.5, 131.3, 130.4, 129.4, 129.3, 127.9, 127.8, 126.5, 126.5, 126.4, 126.2, 126.0, 125.4, 124.8, 124.4, 123.6, 121.8, 121.7, 114.6, 68.1, 31.7, 29.3, 25.8, 22.7, 14.1; HRMS (ESI): *m/z* $[M+H]^+$ calcd for $C_{40}H_{35}N_2O_2$: 575.2699 found, 575.2704.



13j

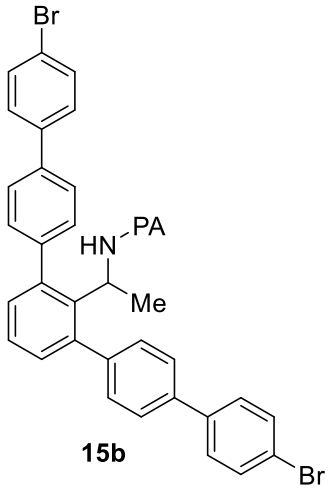
2-([1,1':4',1'':3'',1''':4''',1''''-quinquephenyl]-2''-yl)-2-(picolinamido)ethyl acetate (15a): Following general procedure B, the compound **15a** was obtained after purification by column chromatography on silica gel (EtOAc:hexane = 20:80) as a brown solid (111 mg, 95%, 0.2 mmol scale); R_f = 0.3 (EtOAc:hexane = 20:80); mp 95-97 °C; IR (DCM): 3371, 1676, 1509, 1248, 730 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ_H 8.28–8.27 (1H, m), 8.10 (1H, d, J = 7.8 Hz), 7.99 (1H, d, J = 8.8 Hz), 7.81–7.25 (23H, m), 5.90–5.88 (1H, m), 4.43-4.37 (1H, m), 4.32-4.28 (1H, m), 1.92 (3H, s); $^{13}C\{^1H\}$ NMR (~101 MHz, $CDCl_3$): δ_C 170.7, 163.4, 149.4, 147.8, 142.5, 140.8, 140.7, 140.0, 137.0, 133.5, 130.9, 129.9, 128.8, 127.4, 127.1, 127.1, 127.0, 126.9,



15a

126.8, 125.9, 121.9, 66.4, 50.6, 20.8; HRMS (ESI): *m/z* $[M+H]^+$ calcd for $C_{40}H_{33}N_2O_3$: 589.2491 found, 589.248.

***N*-(1-(4,4''''-Dibromo-[1,1':4',1'':3'',1''':4''',1''''-quinquephenyl]-2''-yl)ethyl)picolinamide (15b):** Following general procedure B, the compound **15b** was obtained

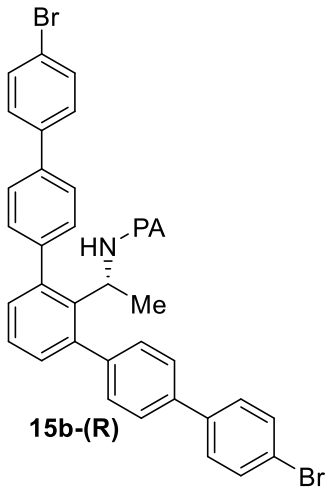


15b

after purification by column chromatography on silica gel (EtOAc:hexane = 20:80) as a pale yellow coloured solid (80 mg, 58%, 0.2 mmol scale); R_f = 0.4 (EtOAc:hexane = 20:80); mp: 120-122 °C; IR (DCM): 3381, 2924, 1673, 1516, 815 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ_H 8.18 (1H, d, *J* = 4.3 Hz), 8.10 (1H, d, *J* = 7.8 Hz), 7.82 (2H, td, J_1 = 7.6 Hz, J_2 = 1.6 Hz), 7.64–7.40 (16H, m), 7.35–7.30 (2H, m), 7.21 (2H, d, *J* = 7.5 Hz), 5.59–5.55 (1H, m), 1.48 (3H, d, *J* = 7.2 Hz); $^{13}C\{^1H\}$ NMR (~101 MHz, $CDCl_3$): δ_C 162.2, 149.2, 147.0, 141.9, 141.2, 139.7, 138.7, 138.5, 137.7, 132.0, 130.8, 130.0, 128.6, 126.6, 126.0, 125.9, 122.3, 121.6, 47.1, 23.6; HRMS (ESI): *m/z* $[M+H]^+$ calcd for $C_{38}H_{29}Br_2N_2O$: 687.0647 found, 687.0652;

The HPLC of compound **15b** was determined using the Daicel Chiralpak IC column, hexane/*i*-PrOH 95:05, flow rate 1.0 mL/min, UV detection at 254 nm, t_R = 50.97 min, t_S = 26.46 min.

(*R*)-*N*-(1-(4,4''''-Dibromo-[1,1':4',1'':3'',1''':4''',1''''-quinquephenyl]-2''-yl)ethyl)picolinamide (15b-(*R*)): Following general procedure B, the compound **15b**-(*R*) was



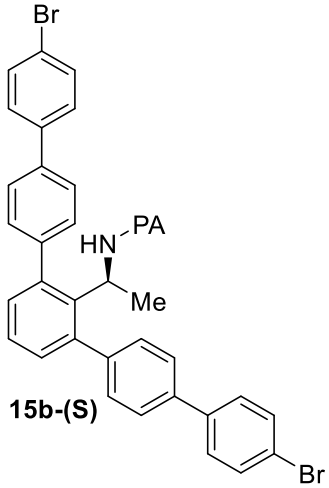
15b-(R)

obtained after purification by column chromatography on silica gel (EtOAc:hexane = 20:80) as a pale yellow coloured solid (90 mg, 66%, 0.2 mmol scale); R_f = 0.4 (EtOAc:hexane = 20:80); mp: 125-127 °C; IR (DCM): 3382, 3054, 1673, 1514, 815 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ_H 8.19 (1H, d, *J* = 4.5 Hz), 8.08 (1H, d, *J* = 7.8 Hz), 7.80–7.28 (20H, m), 7.21 (2H, d, *J* = 7.5 Hz), 5.59–5.55 (1H, m), 1.47 (3H, d, *J* = 7.2 Hz); $^{13}C\{^1H\}$ NMR (~101 MHz, $CDCl_3$): δ_C 162.7, 149.7, 147.6, 141.8, 141.3, 139.7, 138.8, 138.6, 137.1, 131.9, 130.8, 130.1, 128.6, 126.5, 126.0, 125.8, 121.9, 121.6, 46.8, 23.7; HRMS (ESI): *m/z* $[M+H]^+$ calcd for $C_{38}H_{29}Br_2N_2O$: 687.0647 found, 687.0651;

$[\alpha]^{25}_D$ = +34.05 (c = 0.02 g/mL, $CHCl_3$);

The enantiomeric ratio (*er* = 99:1) of compound **15b**-(*R*) was determined by HPLC using the Daicel Chiralpak IC column, hexane/*i*-PrOH 95:05, flow rate 1.0 mL/min, UV detection at 254 nm, t_R = 50.24 min, t_S = 26.57 min.

(*S*)-*N*-(1-(4,4''''-Dibromo-[1,1':4',1'':3'',1''':4''',1''''-quinquephenyl]-2''-yl)ethyl)picolinamide (15b-(*S*)): Following general procedure B, the compound **15b**-(*S*) was



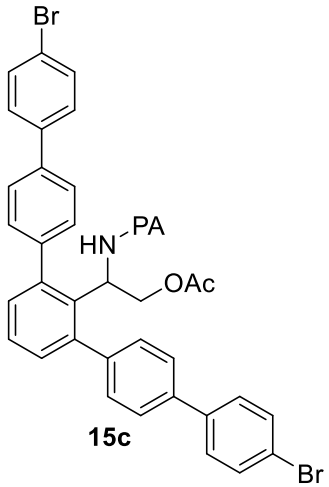
15b-(S)

obtained after purification by column chromatography on silica gel (EtOAc:hexane = 20:80) as a pale yellow coloured solid (90 mg, 66%, 0.2 mmol scale);R_f = 0.4 (EtOAc:hexane = 20:80); IR (DCM): 3381, 2924, 1673, 1516, 815 cm^{-1}; mp: 126-128 ^oC; ^1H NMR (400 MHz, $CDCl_3$): δ_H 8.19 (1H, d, *J* = 4.7 Hz), 8.08 (1H, d, *J* = 7.8 Hz), 7.80–7.28 (20H, m), 7.20 (2H, d, *J* = 7.4 Hz), 5.59–5.55 (1H, m), 1.47 (3H, d, *J* = 7.2 Hz); $^{13}C\{^1H\}$ NMR (~101 MHz, $CDCl_3$): δ_C 162.7, 149.7, 147.6, 141.9, 141.3, 139.7, 138.8, 138.6, 137.1, 131.9, 130.8, 130.1, 128.6, 126.5, 126.0, 125.8, 121.8, 121.6, 46.8, 23.7; HRMS (ESI): *m/z* $[M+H]^+$ calcd for $C_{38}H_{29}Br_2N_2O$: 687.0647 found, 687.0647;

$[\alpha]^{25}_D$ = -14.02 (c = 0.02 g/mL, $CHCl_3$);

The enantiomeric ratio (*er* = 99:1) of compound **15b**-(*S*) was determined by HPLC using the Daicel Chiralpak IC column, hexane/*i*-PrOH 95:05, flow rate 1.0 mL/min, UV detection at 254 nm, t_R = 50.51, min t_S = 26.13 min.

2-(4,4''''-Dibromo-[1,1':4',1'':3'',1''':4''',1''''-quinquephenyl]-2''-yl)-2-(picolinamido)ethyl acetate (15c): Following general procedure B, the compound **15c** was



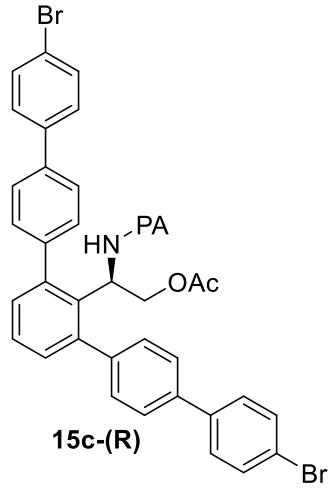
15c

obtained after purification by column chromatography on silica gel (EtOAc:hexane = 20:80) as a brown solid (99 mg, 66%, 0.2 mmol scale); R_f = 0.3 (EtOAc:hexane = 20:80); mp 107-109 ^oC; IR (DCM): 3371, 1675, 1512, 1483, 1227 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ_H 8.24–8.23 (1H, m), 8.08 (1H, d, *J* = 7.8 Hz), 7.92 (1H, d, *J* = 8.8 Hz), 7.79 (1H, td, J_1 = 7.7 Hz, J_2 = 1.7 Hz), 7.71–7.42 (15H, m), 7.39–7.31 (3H, m), 7.24 (2H, d, *J* = 7.5 Hz), 5.86–5.80 (1H, m), 4.38–4.33 (1H, m), 4.27–4.23 (1H, m), 1.90 (3H, s); $^{13}C\{^1H\}$ NMR (~101 MHz, $CDCl_3$): δ_C 170.7, 163.4, 149.3, 147.7, 142.3, 141.1, 139.6, 138.8, 137.1, 133.4, 131.9, 130.9, 130.0, 128.7, 128.6, 126.9, 126.7, 126.0,

121.9, 121.6, 66.2, 50.6, 20.8; HRMS (ESI): *m/z* $[M+H]^+$ calcd for $C_{40}H_{31}Br_2N_2O_3$: 745.0701 found, 745.0707;

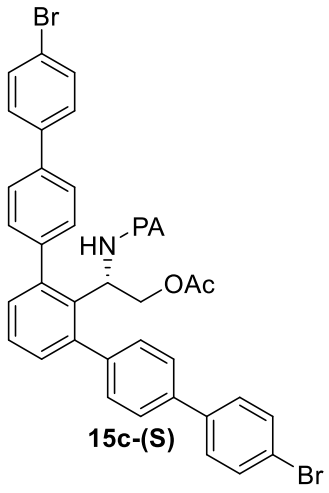
The HPLC of compound **15c** was determined using the Daicel Chiralpak IC column, hexane/*i*-PrOH (90:10), flow rate 1.0 mL/min, UV detection at 254 nm, t_R = 20.37 min, t_S = 31.08 min.

(*R*)-2-(4,4''''-Dibromo-[1,1':4',1'':3'',1''':4''',1''''-quinquephenyl]-2''-yl)-2-(picolinamido)ethyl acetate (15c-(*R*)): Following general procedure B, the compound **15c-(*R*)** was obtained after purification by column chromatography on silica gel (EtOAc:hexane = 20:80) as a brown coloured solid (116 mg, 78%, 0.2 mmol scale); R_f = 0.4 (EtOAc:hexane = 20:80); mp 104-106 °C; IR (DCM): 3368, 1740, 1677, 1514, 1231 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ_H 8.26-8.25 (1H, m), 8.10 (1H, d, J = 7.8 Hz), 7.96 (1H, d, J = 8.8 Hz), 7.79 (1H, td, J_1 = 7.8 Hz, J_2 = 1.5 Hz), 7.75–7.31 (17H, m), 7.28–7.25 (3H, m), 5.89–5.84 (1H, m), 4.42–4.36 (1H, m), 4.30–4.26 (1H, m), 1.91 (3H, s); $^{13}C\{^1H\}$ NMR (~101 MHz, $CDCl_3$): δ_C 170.7, 163.4, 149.3, 147.7, 142.3, 141.1, 139.5, 138.8, 137.0, 133.3, 131.9, 130.9, 130.0, 128.6, 126.9, 126.6, 126.0, 121.9, 121.6, 66.2, 50.6, 20.8; HRMS (ESI): *m/z* $[M+H]^+$ calcd for $C_{40}H_{31}Br_2N_2O_3$: 745.0701 found, 745.0701; $[\alpha]^{25}_D$ = +16.02 (c = 0.02 g/mL, $CHCl_3$);



The enantiomeric ratio (*er* = 99:1) of compound 1**5c**-(*R*) was determined by HPLC using the Daicel Chiralpak IC column, hexane/*i*-PrOH (90:10), flow rate 1.0 mL/min, UV detection at 254 nm, t_R = 20.44 min, t_S= 30.38 min.

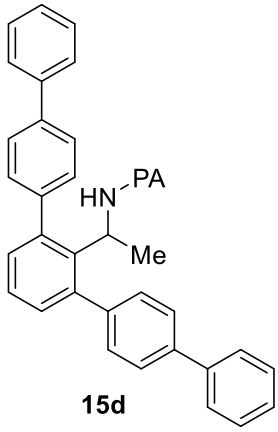
(*S*)-2-(4,4''''-Dibromo-[1,1':4',1'':3'',1''':4''',1''''-quinquephenyl]-2''-yl)-2-(picolinamido)ethyl acetate (15c-(*S*)): Following general procedure B, the compound **15c**-(*S*) was obtained after purification by column chromatography on silica gel (EtOAc:hexane = 20:80) as a brown coloured solid (114 mg, 77%, 0.2 mmol scale); R_f = 0.3 (EtOAc:hexane = 20:80); mp 102-104 °C; IR (DCM): 3380, 3058, 1738, 1676, 1512 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ_H 8.26-8.25 (1H, m), 8.10 (1H, d, J = 7.8 Hz), 7.96 (1H, d, J = 8.8 Hz), 7.79 (1H, td, J_1 = 7.7 Hz, J_2 = 1.3 Hz), 7.75–7. 31 (18H, m), 7.28–7.25 (2H, m), 5.89–5.84 (1H, m), 4.42–4.36 (1H, m), 4.30–4.26 (1H, m), 1.91 (3H, s); $^{13}C\{^1H\}$ NMR (~101 MHz, $CDCl_3$): δ_C 170.6, 163.3, 149.3, 147.7, 142.3, 141.1,



139.5, 138.7, 137.0, 133.3, 131.9, 130.9, 130.0, 128.6, 126.8, 126.6, 125.9, 121.8, 121.6, 66.2, 50.6, 20.8; HRMS (ESI): *m/z* $[M+H]^+$ calcd for $C_{40}H_{31}Br_2N_2O_3$: 745.0701 found, 745.0702; $[\alpha]^{25}{}_D$ = -10.10 (c = 0.02 g/mL, $CHCl_3$);

The enantiomeric ratio (*er* = 99:1) of compound 1**5c**-(*S*) was determined by HPLC using the Daicel Chiralpak IC column, hexane/*i*-PrOH (90:10), flow rate 1.0 mL/min, UV detection at 254 nm, t_R = 20.37 min, t_S= 31.09 min.

***N*-(1-([1,1':4',1'':3'',1''':4''',1''''-Quinquephenyl]-2''-yl)ethyl)picolinamide (15d):**

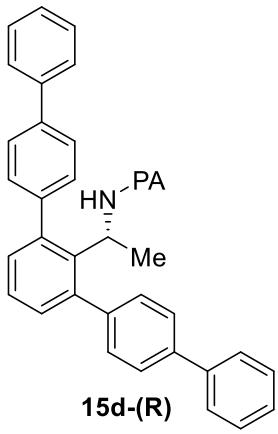


15d

Following general procedure B, the compound **15d** was obtained after purification by column chromatography on silica gel (EtOAc:hexane = 20:80) as a colourless solid (85 mg, 80%, 0.2 mmol scale); R_f = 0.4 (EtOAc:hexane = 20:80); mp: 150-152 ^oC; IR (DCM): 3384, 3055, 1674, 1515, 739 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ_H 8.22–8.20 (1H, m), 8.10 (1H, d, *J* = 7.8), 7.82–7.74 (2H, m), 7.73–7.28 (20H, m), 7.25–7.21 (2H, m), 5.64–5.58 (1H, m), 1.51–1.48 (3H, m); $^{13}C\{^1H\}$ NMR (~101 MHz, $CDCl_3$): δ_C 162.5, 149.6, 147.4, 141.5, 140.8, 139.8, 138.9, 137.3, 131.9, 130.8, 129.9, 128.8, 128.7, 127.3, 127.1, 126.8, 125.9, 125.8, 122.0, 47.0, 23.6; HRMS (ESI): *m/z* $[M+H]^+$ calcd for $C_{38}H_{31}N_2O$: 531.2436 found, 531.2436;

The HPLC of compound **15d** was determined using the Daicel Chiralpak IA column, hexane/*i*-PrOH 50:50, flow rate 1.0 mL/min, UV detection at 254 nm, t_R = 4.69 min, t_S = 6.51 min.

***(R)*-*N*-(1-([1,1':4',1'':3'',1''':4''',1''''-Quinquephenyl]-2''-yl)ethyl)picolinamide (15d-(*R*)):**



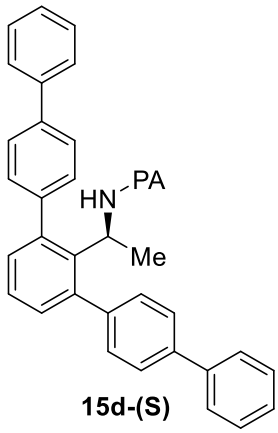
15d-(R)

Following general procedure B, the compound **15d**-(*R*) was obtained after purification by column chromatography on silica gel (EtOAc:hexane = 20:80) as a colourless solid (92 mg, 87%, 0.2 mmol scale); R_f = 0.4 (EtOAc:hexane = 20:80); mp: 158-160 ^oC; IR (DCM): 1673, 1515, 1266, 736 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ_H 8.25-8.24 (1H, m), 8.13 (1H, d, *J* = 7.8 Hz), 7.86–7.47 (18H, m), 7.44–7.40 (2H, m), 7.38–7.25 (4H, m), 5.68–5.64 (1H, m), 1.53 (3H, d, *J* = 7.2 Hz); $^{13}C\{^1H\}$ NMR (~101 MHz, $CDCl_3$): δ_C 162.7, 149.7, 147.6, 141.5, 140.9, 139.8, 138.9, 137.1, 130.8, 130.0, 128.9, 127.4, 127.1, 126.8, 126.0, 125.8, 121.9, 46.9, 23.7; HRMS (ESI): *m/z* $[M+H]^+$ calcd for $C_{38}H_{31}N_2O$: 531.2436 found, 531.2441;

$[\alpha]^{25}{}_D$ = -58.08 (c = 0.02 g/mL, $CHCl_3$);

The enantiomeric ratio (*er* = 95:5) of compound **15d**-(*R*) was determined by HPLC using the Daicel Chiralpak IA column, hexane/*i*-PrOH 50:50, flow rate 1.0 mL/min, UV detection at 254 nm, t_R = 4.71, min t_S = 6.55 min.

***(S)*-*N*-(1-([1,1':4',1'':3'',1''':4''',1''''-Quinquephenyl]-2''-yl)ethyl)picolinamide (15d-(*S*)):**



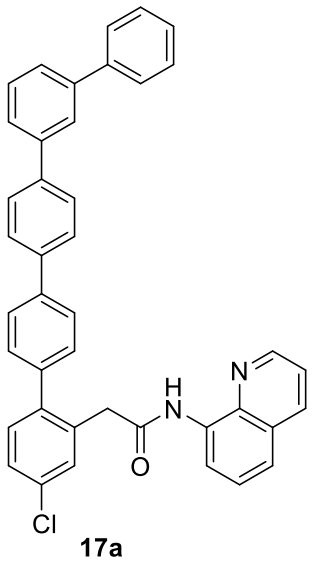
15d-(S)

Following general procedure B, the compound **15d**-(*S*) was obtained after purification by column chromatography on silica gel (EtOAc:hexane = 20:80) as a colourless solid (75 mg, 71%, 0.2 mmol scale); R_f = 0.4 (EtOAc:hexane = 20:80); mp: 152-154 ^oC; IR (DCM): 1673, 1515, 1266, 736 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ_H 8.23–8.22 (1H, m), 8.10 (1H, d, *J* = 7.8 Hz), 7.81–7.56 (11H, m), 7.53-7.46 (6H, m), 7.43–7.38 (3H, m), 7.36–7.28 (2H, m), 7.24 (2H, d, *J* = 7.2 Hz), 5.65–5.61 (1H, m), 1.50 (3H, d, *J* = 7.2 Hz); $^{13}C\{^1H\}$ NMR (~101 MHz, $CDCl_3$): δ_C 162.8, 149.8, 147.7, 141.5, 140.9, 139.8, 138.9, 137.1, 130.8, 130.0, 128.9, 127.4, 127.1, 126.8, 126.0, 125.8, 121.9, 46.9, 23.7; HRMS (ESI): *m/z* $[M+H]^+$ calcd for $C_{38}H_{31}N_2O$: 531.2436 found, 531.2439;

$[\alpha]^{25}_D$ = +40.06 (c = 0.02 g/mL, $CHCl_3$);

The enantiomeric ratio (*er* = 95:5) of compound **15d**-(*S*) was determined by HPLC using the Daicel Chiralpak IA column, hexane/*i*-PrOH 50:50, flow rate 1.0 mL/min, UV detection at 254 nm, t_R = 4.70, min t_S = 6.50 min.

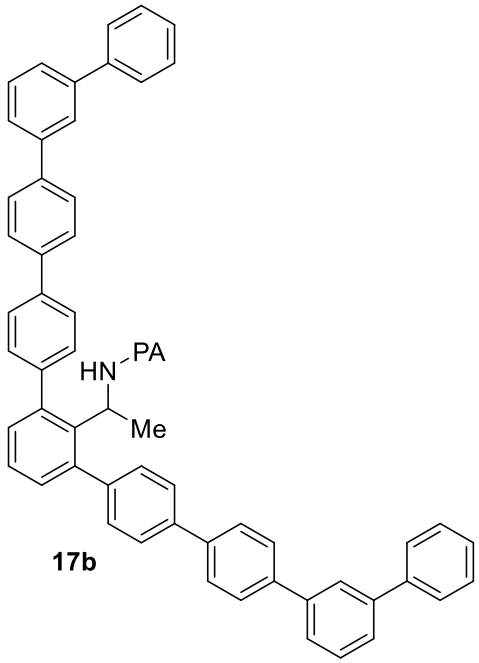
2-(4''''-Chloro-[1,1':3',1'':4'',1''':4''',1''''-quinquephenyl]-2''''-yl)-*N*-(quinolin-8-yl)acetamide (17a): Following general procedure C, the compound **17a** was obtained after purification by column chromatography on silica gel (EtOAc:hexane = 20:80) as a colourless solid (54 mg, 90%, 0.1 mmol scale); R_f = 0.4 (EtOAc:hexane = 20:80); mp: 154-156 ^oC; IR (DCM): 3333, 2997, 1733, 1241, 752 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ_H 9.82 (1H, s), 8.77 (1H, dd, J_1 = 7.0 Hz, J_2 = 1.5 Hz), 8.71 (1H, dd, J_1 = 4.2 Hz, J_2 = 1.6 Hz), 8.15 (1H, dd, J_1 = 8.3 Hz, J_2 = 1.6 Hz), 7.90 (1H, s), 7.76–7.61 (11H, m), 7.59–7.49 (7H, m), 7.44–7.40 (3H, m), 7.36 (1H, d, *J* = 8.2 Hz), 3.90 (2H, s); $^{13}C\{^1H\}$ NMR (~101 MHz, $CDCl_3$): δ_C 168.9, 148.2, 141.9, 141.2, 140.8, 140.2, 139.8, 139.6, 139.1, 138.4, 136.3, 134.4, 134.3, 133.7, 131.7, 130.8, 129.8, 129.3, 128.9, 127.9, 127.6, 127.5, 127.4, 127.4, 127.1, 127.3, 126.3, 126.0,



17a

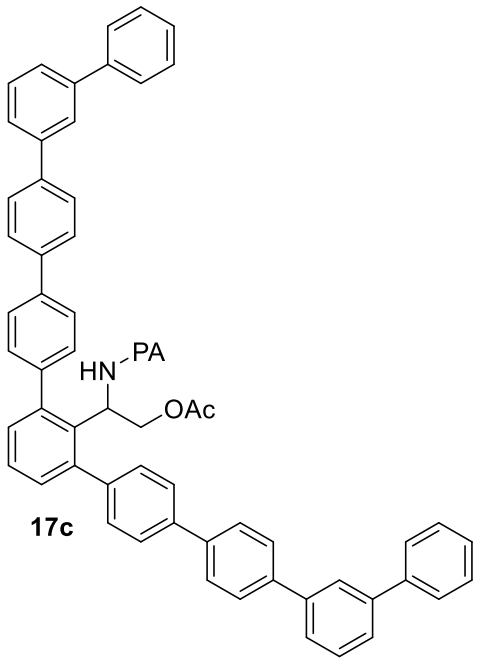
121.8, 121.6, 116.4, 42.5; HRMS (ESI): *m/z* $[M+H]^+$ calcd for $C_{41}H_{30}ClN_2O$: 601.2047 found, 601.2048.

Compound 17b: Following general procedure C, the compound **17b** was obtained after purification by column chromatography on silica gel (EtOAc:hexane = 20:80) as a colourless solid (74 mg, 89%, 0.1 mmol scale); R_f = 0.5 (EtOAc:hexane = 20:80); mp: 105-107 °C; IR (DCM): 3378, 1672, 1510, 1265, 741 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ_H 8.27 (1H, d, *J* = 4.5 Hz), 8.13 (1H, d, *J* = 7.8 Hz), 7.94 (2H, s), 7.86–7.78 (11H, m), 7.74–7.70 (9H, m), 7.67–7.51 (12H, m), 7.43 (2H, t, *J* = 7.4 Hz), 7.38–7.31 (2H, m), 7.27 (2H, d, *J* = 7.4 Hz), 5.68–5.64 (1H, m), 1.53 (3H, d, *J* = 7.2 Hz); $^{13}C\{^1H\}$ NMR (~101 MHz, $CDCl_3$): δ_C 162.7, 149.7, 147.6, 141.9, 141.6, 141.5, 141.2, 141.2, 140.0, 139.9, 139.2, 138.9, 137.2, 130.8, 130.0, 129.3, 128.9, 127.7, 127.5, 127.3, 126.7, 126.3, 126.1, 126.0, 126.0, 125.8, 121.9, 46.9, 23.7; HRMS (ESI): *m/z* $[M+H]^+$ calcd for $C_{62}H_{47}N_2O$: 835.3688 found, 835.3713.



17b

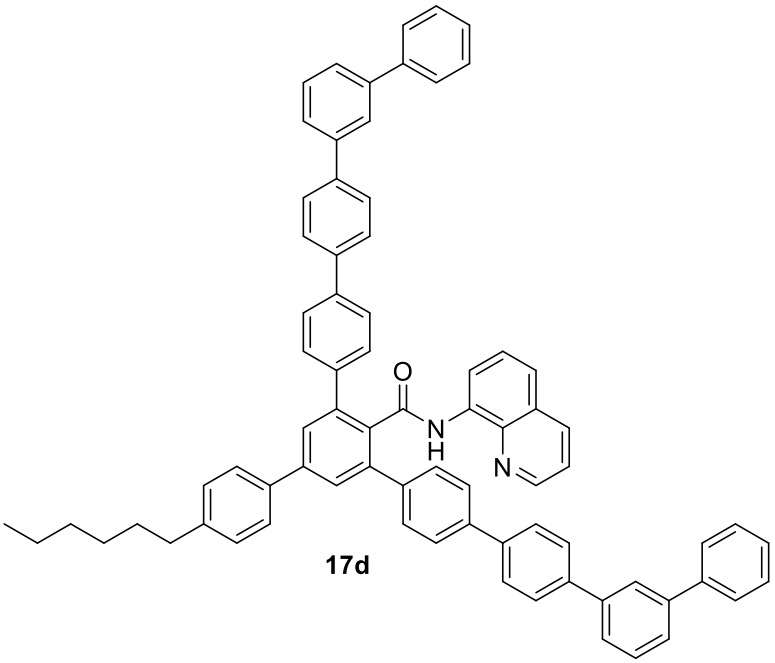
Compound 17c: Following general procedure C, compound **17c** was obtained after purification by column chromatography on silica gel (EtOAc:hexane = 20:80) as a colourless solid (26 mg, 29%, 0.1 mmol scale); R_f = 0.5 (EtOAc:hexane = 20:80); mp: 183-185; IR (DCM): 3382, 1672, 1511, 1272, 735 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ_H 8.31–8.30 (1H, m), 8.12 (1H, dd, J_1 = 7.8 Hz, J_2 = 0.8 Hz), 8.00 (1H, d, *J* = 8.0 Hz), 7.93 (2H, s), 7.82–7.69 (20H, m), 7.66-7.63 (3H, m), 7.61–7.57 (3H, m), 7.54-7.50 (5H, m), 7.44–7.38 (4H, m), 7.36–7.33 (1H, m), 7.30 (1H, m), 5.93–5.89 (1H, m), 4.44–4.39 (1H, m), 4.34–4.30 (1H, m), 1.93 (3H, s); $^{13}C\{^1H\}$ NMR (~101 MHz, $CDCl_3$): δ_C 170.8, 163.5, 149.4, 147.8, 142.5, 141.9, 141.2, 141.2, 141.0, 140.1, 139.8, 139.5, 137.1, 133.5, 131.0, 130.0, 129.3, 128.9, 127.7, 127.6, 127.5, 127.3, 126.9, 126.8, 126.3, 126.1, 126.0, 126.0,



17c

121.9, 66.5, 50.7, 20.9; HRMS (ESI): *m/z* $[M+H]^+$ calcd for $C_{64}H_{49}N_2O_3$: 893.3743 found, 893.3747.

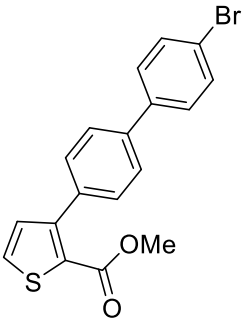
Compound 17d: Following general procedure C, compound **17d** was obtained after



17d

purification by column chromatography on silica gel (EtOAc:hexane = 20:80) as a colourless solid (51 mg, 72%, 0.07 mmol scale); R_f = 0.5 (EtOAc:hexane = 20:80); mp: 124-126 °C; IR (DCM): 3395, 3031, 1680, 1519, 1387 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ_H 9.89 (1H, s), 8.71 (1H, dd, J_1 = 7.5 Hz, J_2 = 1.1 Hz), 8.63 (1H, dd, J_1 = 4.2 Hz, J_2 = 1.6 Hz), 8.05 (1H, dd, J_1 = 8.3 Hz, J_2 = 1.5 Hz), 7.90 (2H, s), 7.86 (2H, s), 7.81 (4H, d, J = 8.2 Hz), 7.75–7.71 (10H, m), 7.66–7.39 (24H, m), 7.33 (1H, dd, J_1 = 8.2 Hz, J_2 = 4.2 Hz), 2.76 (2H, t, J = 7.6 Hz), 1.78–1.74 (2H, m), 1.49–1.39 (6H, m), 0.99 (3H, t, J = 6.9 Hz); $^{13}C\{^1H\}$ NMR (~101 MHz, $CDCl_3$): δ_C 167.7, 147.9, 143.0, 142.4, 141.8, 141.2, 141.1, 140.8, 140.0, 139.7, 139.6, 138.4, 137.3, 136.0, 134.6, 134.4, 129.2, 129.1, 128.9, 128.8, 128.1, 127.7, 127.5, 127.4, 127.3, 127.2, 127.0, 126.2, 126.0, 121.7, 121.4, 116.6, 35.7, 31.8, 31.5, 29.1, 22.7, 14.2; HRMS (ESI): *m/z* $[M+H]^+$ calcd for $C_{76}H_{61}N_2O$: 1017.4784 found, 1017.4783.

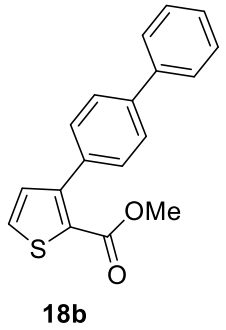
Methyl 3-(4'-bromo-[1,1'-biphenyl]-4-yl)thiophene-2-carboxylate (18a): Following



18a

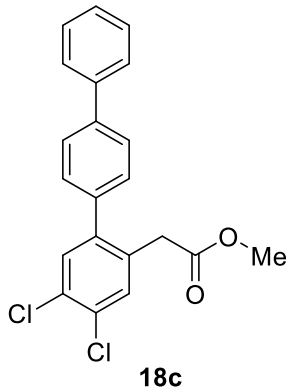
general procedure F, the compound **18a** was obtained after purification by column chromatography on silica gel (EtOAc:hexane = 20:80) as a semi-solid (58 mg, 78%, 0.2 mmol scale); R_f = 0.7 (EtOAc:hexane = 20:80); mp: 141-143 °C; IR (DCM): 3054, 1710, 1261, 726 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ_H 7.64–7.52 (9H, m), 7.15 (1H, d, J = 5.1 Hz), 3.83 (3H, s); $^{13}C\{^1H\}$ NMR (~101 MHz, $CDCl_3$): δ_C 162.5, 148.2, 139.7, 139.5, 135.0, 131.9, 131.5, 130.5, 129.9, 128.7, 126.9, 126.4, 121.7, 52.0; HRMS (ESI): *m/z* $[M+Na]^+$ calcd for $C_{18}H_{13}BrNaO_2S$: 394.9717 found, 394.9707.

Methyl 3-([1,1'-biphenyl]-4-yl)thiophene-2-carboxylate (18b): Following general procedure F, the compound **18b** was obtained after purification by column chromatography on silica gel (EtOAc:hexane = 20:80) as a colourless solid (104 mg, 71%, 0.5 mmol scale); R_f = 0.7 (EtOAc:hexane = 20:80); IR (DCM): 3054, 1710, 1261, 726 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ_H 7.70-7.67 (4H, m), 7.60-7.55 (3H, m), 7.51-7.47 (2H, m), 7.42-7.38 (1H, m), 7.17 (1H, d, J = 5.1 Hz), 3.84 (3H, s); $^{13}C\{^1H\}$ NMR (~101 MHz, $CDCl_3$): δ_C 162.5, 148.4, 140.8, 134.6, 131.9, 131.6, 130.4, 129.9, 129.8, 127.4, 127.2, 126.8, 126.6, 126.4, 52.0; HRMS (ESI): *m/z* $[M+Na]^+$ calcd for $C_{18}H_{14}NaO_2S$: 317.0612 found, 317.0610.



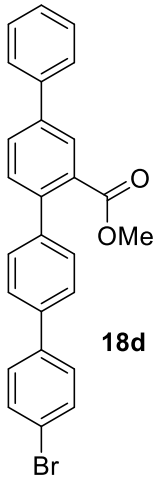
18b

Methyl 2-(4,5-dichloro-[1,1':4',1''-terphenyl]-2-yl)acetate (18c): Following general procedure F, The compound **18c** was obtained after purification by column chromatography on silica gel (EtOAc:hexanes = 05:95) as a colourless solid (112 mg, 74%, 0.41 mmol scale); R_f = 0.5 (EtOAc:hexane = 05:95); mp: 120-122 °C; IR (DCM): 3060, 1266, 727 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ_H 7.64-7.55 (4H, m), 7.47-7.31 (7H, m), 3.64 (3H, s), 3.57 (2H, s); $^{13}C\{^1H\}$ NMR (~101 MHz, $CDCl_3$): δ_C 171.3, 141.9, 140.7, 140.3, 137.6, 132.1, 131.8, 131.7, 131.4, 131.1, 129.3, 128.8, 127.5, 127.1, 127.0, 52.1, 37.9; HRMS (ESI): *m/z* $[M+Na]^+$ calcd for $C_{21}H_{16}Cl_2NaO_2$: 393.0425; found: 393.0420.

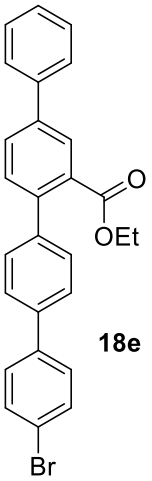


18c

Methyl 4-bromo-[1,1':4',1'':4'',1'''-quaterphenyl]-2''-carboxylate (18d): Following general procedure F, The compound **18d** was obtained after purification by column chromatography on silica gel (EtOAc:hexanes = 05:95) as a colourless solid; (58 mg, 50%, 0.26 mmol scale); R_f = 0.5 (EtOAc:hexane = 05:95); mp: 173-175 °C; IR (DCM): 1724, 1263, 738 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ_H 8.09 (1H, d, J = 1.9 Hz), 7.76 (1H, dd, J_1 = 8.0 Hz, J_2 = 2.0 Hz), 7.66-7.56 (6H, m), 7.52-7.37 (8H, m), 3.71 (3H, s); $^{13}C\{^1H\}$ NMR (~101 MHz, $CDCl_3$): δ_C 168.9, 140.7, 140.3, 140.2, 139.5, 139.5, 138.7, 131.9, 131.2, 131.0, 129.8, 128.9, 128.6, 128.6, 127.8, 127.0, 126.5, 121.6, 52.1; HRMS (ESI): *m/z* $[M+Na]^+$ calcd for $C_{26}H_{19}BrNaO_2$: 465.0466; found: 465.0451.



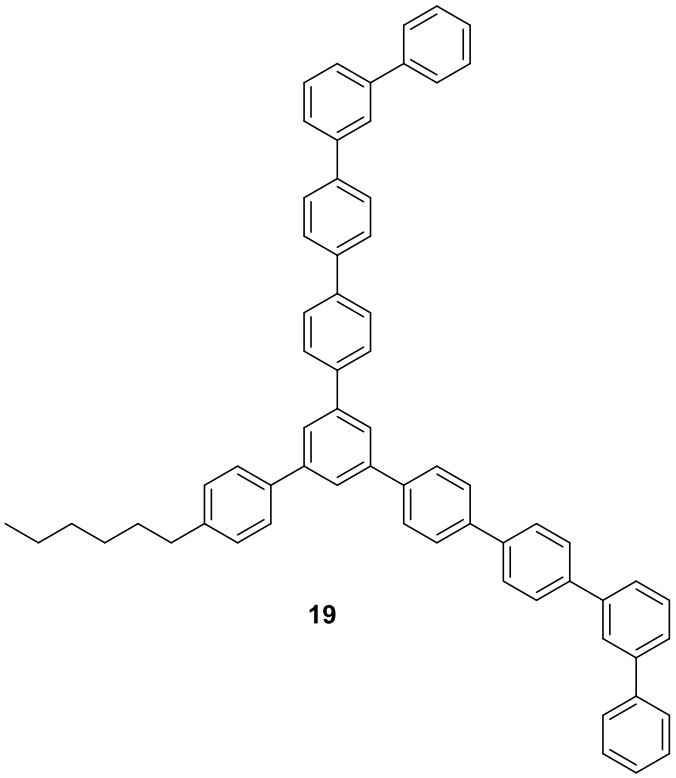
18d



18e

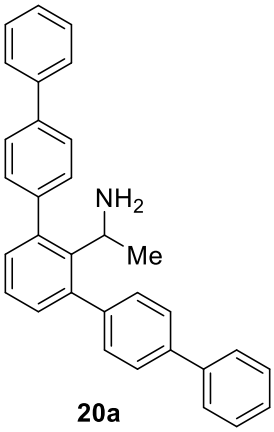
Ethyl 4-bromo-[1,1':4',1'':4'',1'''-quaterphenyl]-2'''-carboxylate (18e): Following general procedure F, The compound **18e** was obtained after purification by column chromatography on silica gel (EtOAc:hexanes = 05:95) as a colourless solid; (55 mg, 60%, 0.2 mmol scale); R_f = 0.5 (EtOAc:hexane = 05:95); mp: 155-157 ^oC; IR (DCM): 1716, 1263, 732 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ_H 8.09 (1H, d, J = 1.9 Hz), 7.78 (1H, dd, J_1 = 8.0 Hz, J_2 = 2.0 Hz), 7.69-7.67 (2H, m), 7.63-7.58 (4H, m), 7.53-7.41 (8H, m), 4.17 (2H, q, J = 7.2 Hz), 1.07 (3H, t, J = 7.1 Hz); $^{13}C\{^1H\}$ NMR (~101 MHz, $CDCl_3$): δ_C 168.7, 140.6, 140.5, 140.3, 139.7, 139.6, 138.8, 131.9, 131.6, 131.1, 129.7, 129.0, 128.9, 128.6, 128.5, 127.8, 127.1, 126.5, 121.6, 61.1, 13.7; HRMS (ESI): *m/z* $[M+Na]^+$ calcd for $C_{27}H_{21}BrNaO_2$: 479.0623; found: 479.0613.

Compound 19: Following general procedure E, compound **19** was obtained after purification by column chromatography on silica gel (EtOAc:hexane = 20:80) as a colourless solid (11 mg, 33%, 0.04 mmol scale); R_f = 0.6 (EtOAc:hexane = 20:80); mp: 141-143 ^oC; IR (DCM): 3046, 1668, 1531, 1261,730 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ_H 7.89 (2H, s), 7.78–7.61 (27H, m), 7.57–7.48 (6H, m), 7.43–7.39 (2H, m), 7.32–7.28 (4H, m, J = 8.1 Hz), 2.69 (2H, 2t, J = 7.8 Hz), 1.70–1.66 (2H, m), 1.41–1.26 (6H, m), 0.92 (3H, t, J = 6.7 Hz); $^{13}C\{^1H\}$ NMR (~101 MHz, $CDCl_3$): δ_C 143.2, 142.6, 141.9, 141.2, 141.2, 140.7, 140.2, 140.0, 139.6, 139.6, 137.1, 129.3, 129.1, 128.8, 127.8, 127.7, 127.7, 127.5, 127.5, 127.3, 127.2, 127.1, 126.3, 126.0, 126.0, 35.7, 31.8, 31.5, 29.0, 22.6, 14.1; HRMS (ESI): *m/z* $[M-H]^+$ calcd for $C_{66}H_{53}$: 845.4147; found: 845.4128.



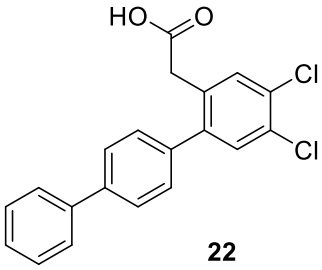
19

1-([1,1':4',1'':3'',1''':4''',1''''-Quinquephenyl]-2''-yl)ethan-1-amine (20a): Following general procedure D, the compound **20a** was obtained after purification by column chromatography on silica gel (EtOAc:hexane = 40:60) as a colourless solid (21 mg, 55%, 0.09 mmol scale); R_f = 0.3 (EtOAc:hexane = 20:80); mp: 140-142 ^oC; IR (DCM): 2926, 1486, 1385, 841, 760 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ_H 7.69–7.67 (7H, m), 7.55-7.45 (9H, m), 7.43–7.32 (3H, m), 7.24 (2H, d, J = 7.2 Hz), 4.40 (1H, q, J = 7.0 Hz), 2.60–2.59 (2H, m), 1.30 (3H, d, J = 7.0 Hz); $^{13}C\{^1H\}$ NMR (~101 MHz, $CDCl_3$): δ_C 141.6, 141.3, 140.6, 140.2, 130.9, 130.1, 128.9, 127.5, 127.2, 127.0, 126.8, 125.8, 49.2, 25.0; HRMS (ESI): *m/z* $[M+H]^+$ calcd for $C_{32}H_{28}N$: 426.2222 found, 426.2232.



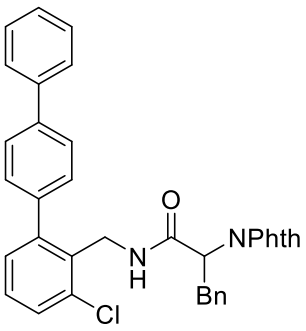
20a

2-(4,5-Dichloro-[1,1':4',1''-terphenyl]-2-yl)acetic acid (22): Following general procedures F and G1, The compound **22** was obtained after purification by column chromatography on silica gel (EtOAc:hexanes = 20:80) as a colourless solid (50 mg, 67%, 0.21 mmol scale); R_f = 0.5(EtOAc:hexane = 20:80); mp: 198-200 ^oC; IR (DCM): 3055, 1264, 731 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ_H 7.66-7.57 (4H, m), 7.48-7.33 (7H, m), 3.63 (2H, s); $^{13}C\{^1H\}$ NMR (~101 MHz, $CDCl_3$): δ_C 171.1, 142.1, 140.9, 140.3, 137.4, 132.2, 131.8, 131.5, 131.4, 131.1, 129.4, 128.9, 127.6, 127.2, 127.1, 37.8; HRMS (ESI): *m/z* $[M-H]^+$ calcd for $C_{20}H_{13}Cl_2O_2$: 355.0293 found, 355.0288.



22

***N*-((3-Chloro-[1,1':4',1''-terphenyl]-2-yl)methyl)-2-(1,3-dioxoisoindolin-2-yl)-3-phenylpropanamide (21-(DL)):** Following general procedure D and H, the compound **21-(DL)** was obtained after purification by column chromatography on silica gel (EtOAc:hexane = 50:50) as a colourless solid (39 mg, 63%, 0.11 mmol scale); R_f = 0.2 (EtOAc:hexane = 20:80); mp: 184-186 ^oC; IR (DCM): 3028, 1712, 1521, 1383, 755 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ_H 7.75-7.72 (2H, m), 7.67-7.64 (2H, m), 7.60 (4H, t, J = 8.6 Hz), 7.49-7.45 (2H, t, J = 7.2 Hz), 7.41-7.37 (2H, m), 7.34-7.30 (3H, m), 7.23 (1H, dd, J_1 = 7.6 Hz, J_2 = 1.0 Hz), 7.16-7.11 (5H, m), 6.33 (1H, s), 5.09 (1H, dd, J_1 = 6.7 Hz, J_2 = 10.0 Hz), 4.66 (1H, dd, J_1 = 14.1 Hz, J_2 = 5.2 Hz), 4.56 (1H, dd, J_1 = 14.1 Hz, J_2 = 5.2 Hz), 3.55-3.52 (2H, m); $^{13}C\{^1H\}$ NMR (~101 MHz, $CDCl_3$): δ_C 167.9, 167.6, 144.7, 140.6, 140.4, 138.9, 136.7, 135.7, 134.2, 132.5, 131.4, 129.3,

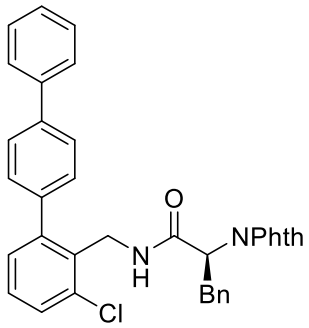


21-(DL)

129.1, 129.0, 128.9, 128.8, 128.6, 127.5, 127.3, 127.2, 127.2, 126.9, 123.5, 55.9, 39.9, 34.8; HRMS (ESI): *m/z* $[M+H]^+$ calcd for $C_{36}H_{28}ClN_2O_3$: 571.1788 found, 571.1796.

The HPLC of compound **21-**(DL) was determined using the Daicel Chiralpak IA column, hexane/*i*-PrOH 50:50, flow rate 1.0 mL/min, UV detection at 254 nm, t_D = 13.17 min, t_L = 10.60 min.

(*S*)-*N*-((3-Chloro-[1,1':4',1''-terphenyl]-2-yl)methyl)-2-(1,3-dioxoisoindolin-2-yl)-3-phenylpropanamide 21-(L): Following general procedure D and H, the compound **21**-(L) was obtained after purification by column chromatography on silica gel (EtOAc:hexane = 20:80) as a colourless solid (19 mg, 35%, 0.15 mmol scale); R_f = 0.2 (EtOAc:hexane = 20:80); mp: 178-180 °C; IR (DCM): 3342, 1700, 1523, 1372, 738 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ_H 7.75-7.71 (2H, m), 7.67-7.57 (6H, m), 7.49-7.37 (4H, m), 7.34-7.30 (3H, m), 7.25 (1H, dd, J_1 = 7.6 Hz, J_2 = 1.0 Hz), 7.16-7.10 (5H, m), 6.34 (1H, s), 5.11-5.07 (1H, m), 4.66 (1H, dd, J_1 = 14.1 Hz, J_2 = 5.2 Hz), 4.56 (1H, dd, J_1 = 14.1 Hz, J_2 = 5.2 Hz), 3.55-3.51 (2H, m); $^{13}C\{^1H\}$ NMR (~101 MHz, $CDCl_3$): δ_C 167.9, 167.6, 144.6, 140.5, 140.4, 138.8, 136.6, 135.6, 134.2, 132.4, 131.3, 129.3, 129.1, 129.0, 128.9, 128.8, 128.7, 128.6, 127.4, 127.2, 127.1, 126.9, 123.4, 55.8, 39.9, 34.7; HRMS (ESI): *m/z* $[M+H]^+$ calcd for $C_{36}H_{28}ClN_2O_3$: 571.1788 found, 571.1792.

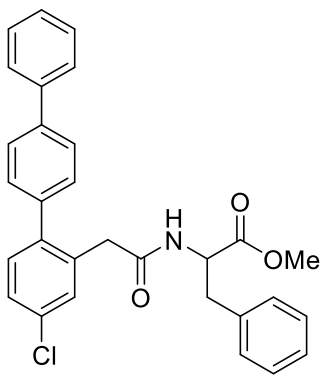


21-(L)

$[\alpha]^{25}_D$ = -67.98 (c = 0.02 g/mL, $CHCl_3$);

The enantiomeric ratio (*er* = 95:5) of compound **21-**(L) was determined by HPLC using the Daicel Chiralpak IA column, hexane/*i*-PrOH 50:50, flow rate 1.0 mL/min, UV detection at 254 nm, t_D = 13.30, min t_L = 10.41 min.

Methyl (2-(4-chloro-[1,1':4',1''-terphenyl]-2-yl)acetyl)phenylalaninate (23-(DL)): Following general procedures G2 and I , the compound **23**-(DL) was obtained after purification by column chromatography on silica gel (EtOAc:hexanes = 20:80) as a colourless solid; (26 mg, 54%, 0.1 mmol scale); R_f = 0.5 (EtOAc:hexane = 20:80); mp: 165-167 °C; IR (DCM): 3286, 1743, 701 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ_H 7.65-7.55 (4H, m), 7.51-7.47 (2H, m), 7.41-7.35 (3H, m), 7.28-7.23 (6H, m), 6.99-6.97 (2H, m), 5.77 (1H, d, *J* = 7.6 Hz), 4.87-4.82 (1H, m), 3.73 (3H, s), 3.53 (2H, d, *J* = 3.2 Hz), 3.13 (1H, dd, J_1 = 14.0 Hz, J_2 = 5.5 Hz), 3.04 (1H, dd, J_1 = 14.0 Hz, J_2 = 5.5 Hz); $^{13}C\{^1H\}$ NMR (~101 MHz, $CDCl_3$): δ_C 171.7, 169.8, 140.6, 140.4, 140.4, 138.5, 135.5,

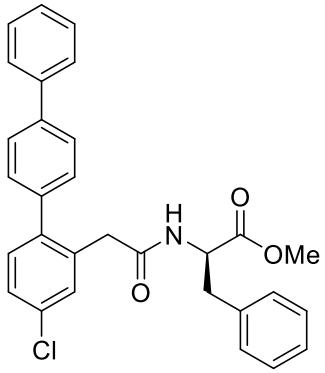


23-DL

133.8, 133.6, 131.9, 131.7, 130.4, 129.5, 129.0, 128.8, 128.7, 127.6, 127.5, 127.2, 127.1, 127.1, 126.9, 53.0, 52.4, 40.7, 37.6; (The NMR indicated that the compound seems to be existing as rotamers); HRMS (ESI): *m/z* $[M+H]^+$ calcd for $C_{30}H_{27}ClNO_3$: 484.1679; found: 484.1682;

The HPLC of compound **23**-(DL) was determined using the Daicel Chiralpak IC column, hexane/*i*- PrOH 70:30, flow rate 1.0 mL/min, UV detection at 254 nm, t_D = 18.18 min, t_L = 19.69 min .

(*R*)-Methyl (2-(4-chloro-[1,1':4',1''-terphenyl]-2-yl)acetyl)-D-phenylalaninate (23-(D)):



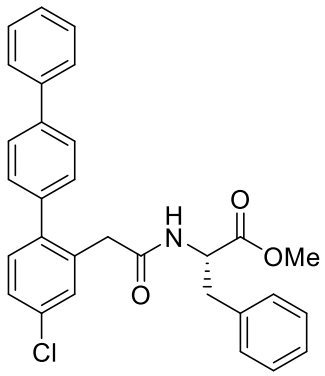
23-(D)

Following general procedures G2 and I , the compound **23**-(D) was obtained after purification by column chromatography on silica gel (EtOAc:hexanes = 20:80) as a colourless solid; (25 mg, 52%, 0.1 mmol scale); R_f = 0.5 (EtOAc:hexane = 20:80); mp: 164-166 ^oC; IR (DCM): 3286, 1742, 701 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ_H 7.65-7.56 (4H, m), 7.51-7.47 (2H, m), 7.42-7.35 (3H, m), 7.28-7.21 (6H, m), 6.98 (2H, dd, J_1 = 7.8 Hz, J_2 = 2.0 Hz), 5.77 (1H, d, J = 7.6 Hz), 4.87-4.82 (1H, m), 3.73 (3H, s), 3.53-3.50 (2H, m), 3.13 (1H, dd, J_1 = 13.9 Hz, J_2 = 5.5 Hz), 3.04 (1H, dd, J_1 = 13.9 Hz, J_2 = 5.5 Hz); $^{13}C\{^1H\}$ NMR (~101 MHz, $CDCl_3$): δ_C 171.7, 169.8, 140.6, 140.4, 140.4, 138.5, 135.5, 133.8, 133.5, 131.9, 131.7, 130.4, 129.5, 129.0, 128.8, 128.6, 127.6, 127.4, 127.2, 127.1, 127.1, 53.0, 52.3, 40.7, 37.5; (The NMR indicated that the compound seems to be existing as rotamers); HRMS (ESI): *m/z* $[M+H]^+$ calcd for $C_{30}H_{27}ClNO_3$: 484.1679; found: 484.1678;

$[\alpha]^{25}{}_D$ = -40.06 (c = 0.01 g/mL, $CHCl_3$);

The enantiomeric ratio (*er* = 99:1) of compound **23**-(D) was determined by HPLC using the Daicel Chiralpak IC column, hexane/*i*-PrOH 70:30, flow rate 1.0 mL/min, UV detection at 254 nm, t_D = 18.37, min t_L = 19.96 min.

(*S*)-Methyl (2-(4-chloro-[1,1':4',1''-terphenyl]-2-yl)acetyl)-L-phenylalaninate (23-(L)):



23-(L)

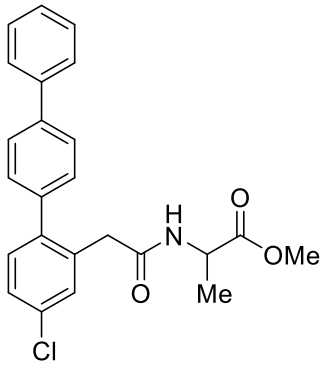
Following general procedures G2 and I , the compound **23**-(L) was obtained after purification by column chromatography on silica gel (EtOAc:hexanes = 20:80) as a colourless solid; (26 mg, 54%, 0.1 mmol scale); R_f = 0.5 (EtOAc:hexane = 20:80); mp: 166-168 ^oC; IR (DCM): 3284, 1742, 700 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ_H 7.65-7.55 (4H, m), 7.51-7.47 (2H, m), 7.41-7.35 (3H, m), 7.28-7.23 (6H, m), 6.98 (2H, dd, J_1 = 7.8 Hz, J_2 = 1.3 Hz), 5.77 (1H, d, J = 7.6 Hz), 4.87-4.82 (1H, m), 3.73 (3H, s), 3.53-3.50 (2H, m), 3.13

(1H, dd, J_1 = 13.9 Hz, J_2 = 5.5 Hz), 3.04 (1H, dd, J_1 = 13.9 Hz, J_2 = 5.5 Hz); $^{13}C\{^1H\}$ NMR (~101 MHz, $CDCl_3$): δ_C 171.7, 169.8, 140.6, 140.4, 140.4, 138.5, 135.5, 133.8, 133.6, 131.9, 131.7, 130.4, 129.5, 129.0, 128.8, 128.7, 127.6, 127.5, 127.2, 127.1, 127.1, 53.0, 52.3, 40.7, 37.5; (The NMR indicated that the compound seems to be existing as rotamers); HRMS (ESI): *m/z* $[M+H]^+$ calcd for $C_{30}H_{27}ClNO_3$: 484.1679; found: 484.1677;

$[\alpha]^{25}{}_D$ = +42.062 (c = 0.01 g/mL, $CHCl_3$);

The enantiomeric ratio (*er* = 99:1) of compound **23-(**L**)** was determined by HPLC using the Daicel Chiralpak IC column, hexane/*i*-PrOH 70:30, flow rate 1.0 mL/min, UV detection at 254 nm, t_D = 18.36, min t_L = 19.83 min.

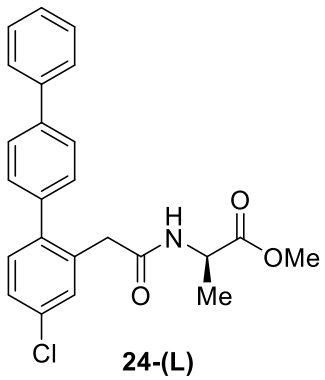
Methyl (2-(4-chloro-[1,1':4',1''-terphenyl]-2-yl)acetyl)alaninate (24-(DL)): Following general procedure G2 and I, the compound **24**-(DL) was obtained after purification by column chromatography on silica gel (EtOAc:hexanes = 20:80) as a colourless solid; (27 mg, 67%, 0.1 mmol scale); R_f = 0.5 (EtOAc:hexane = 20:80); mp: 162-164 °C; IR (DCM): 3299, 1748, 768 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ_H 7.64-7.56 (4H, m), 7.49-7.23 (8H, m), 6.01-5.92 (1H, m), 4.56-4.88 (1H, m), 3.71 (3H, s), 3.55 (2H, s), 1.32 (3H, d, J = 7.2 Hz); $^{13}C\{^1H\}$ NMR (~101 MHz, $CDCl_3$): δ_C 173.1, 169.8, 140.5, 140.4, 140.4, 138.7, 133.9, 133.5, 131.9, 131.6, 130.5, 129.5, 128.8, 127.6, 127.5, 127.1, 127.0, 52.5, 48.1, 40.8, 18.2; (The NMR indicated that the compound seems to be existing as rotamers); HRMS (ESI): *m/z* $[M+H]^+$ calcd for $C_{24}H_{23}ClNO_3$: 408.1366; found: 408.1361;



24-(DL)

The HPLC of compound **24**-(DL) was determined using the Daicel Chiralpak IA column, hexane/*i*-PrOH 80:20, flow rate 1.0 mL/min, UV detection at 254 nm, t_D = 23.29 min, t_L = 25.44 min .

(*S*)-Methyl (2-(4-chloro-[1,1':4',1''-terphenyl]-2-yl)acetyl)alaninate (24-(L)): Following general procedure G2 and I , the compound **24**-(L)was obtained after purification by column chromatography on silica gel (EtOAc:hexanes = 20:80) as a colourless solid; (26 mg, 65%, 0.1 mmol scale); R_f = 0.5 (EtOAc:hexane = 20:80); mp: 161-163 °C; IR (DCM): 3317, 1747, 768 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ_H 7.68-7.60 (4H, m), 7.52-7.47 (2H, m), 7.44-7.34 (5H, m), 7.29-7.27 (1H, m), 5.98 (1H, d, J = 7.0 Hz), 4.59-4.52 (1H, m), 3.73 (3H, s), 3.58 (2H, s), 1.35 (3H, d, J = 7.2 Hz); $^{13}C\{^1H\}$ NMR (~101 MHz, $CDCl_3$): δ_C 173.1, 169.8,

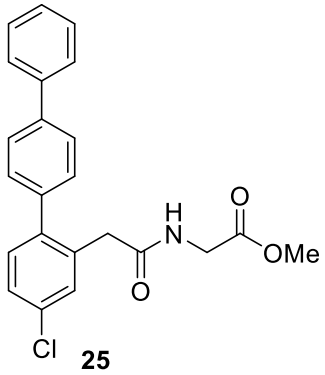


24-(L)

140.6, 140.5, 140.5, 138.8, 134.0, 133.6, 132.0, 131.6, 130.6, 129.6, 128.9, 127.7, 127.5, 127.2, 127.1, 52.4, 48.1, 40.8, 18.2; (The NMR indicated that the compound seems to be existing as rotamers); HRMS (ESI): *m/z* $[M+H]^+$ calcd for $C_{24}H_{23}ClNO_3$: 408.1366; found: 408.1361; $[\alpha]^{25}{}_D$ = +42.174 (c = 0.01 g/mL, $CHCl_3$);

The enantiomeric ratio (*er*= 97:3) of compound **24**-(L) was determined by HPLC using the Daicel Chiralpak IA column, hexane/*i*-PrOH 80:20, flow rate 1.0 mL/min, UV detection at 254 nm, t_D = 23.80, min t_L = 25.98 min.

Methyl (2-(4-chloro-[1,1':4',1''-terphenyl]-2-yl)acetyl)glycinate (25): Following general procedures G and I, the compound **25** was obtained after purification by column chromatography on silica gel (EtOAc:hexane = 20:80) as a colourless solid (21 mg, 72%, 0.075 mmol scale); R_f = 0.2 (EtOAc:hexane = 20:80); mp: 154-156 ^oC; IR (DCM): 3302, 2944, 1757, 1649, 1210 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ_H 7.68–7. 62 (4H, m), 7.53–7.44 (3H, m), 7.41–7.35 (4H, m), 7.31–7.28 (1H, m), 5.91 (1H, s), 4.01 (2H, s), 3.75 (3H, s), 3.59 (2H, s); (The NMR indicated that the compound seems to be existing as rotamers); $^{13}C\{^1H\}$ NMR (~101 MHz, $CDCl_3$): δ_C 170.5, 170.1, 140.7, 140.5, 140.5, 138.7, 133.9, 133.7, 131.7, 130.5, 129.6, 128.9, 127.7, 127.5, 127.2, 127.1, 52.4, 41.4, 40.7; HRMS (ESI): *m/z* $[M+H]^+$ calcd for $C_{23}H_{21}ClNO_3$: 394.1210 found, 394.1209.



25

References and notes

1. For selected reviews on cross-coupling reactions*:* a) Suzuki, A. *Angew. Chem. Int. Ed.* **2011**, *50*, 6722; b) Meijere, A. D.; Bräse, S.; Oestreich, M. *Metal-catalyzed cross-coupling reactions and more,* Wiley-VCH, Weinheim, **2014**; c) Seechurn, C. C. C. J.; Kitching, M. O.; Colacot, T. J.; Snieckus, V. *Angew. Chem. Int. Ed.* **2012**, *51*, 5062; d) Hussain, I.; Capricho, J.; Yawer, M. A. *Adv. Synth. Catal.* **2016**, *358*, 3320; e) Biffis, A.; Centomo, P.; Zotto, A. D.; Zecca, M. *Chem. Rev.* **2018**, *118*, 2249; f) Campeau, L.C.; Hazari, N. *Organometallics* **2019**, *38*, 3; g) Hassan, J.; Sévignon, M.; Gozzi, C.; Schulz, E.; Lamaire, M. *Chem. Rev.* **2002**, *102*, 1359.
2. For selected reviews on bio-active biaryls and application of biaryls in materials: a) Yet, L. *in Privileged Structures in Drug Discovery*, Wiley, Hoboken, **2018**, Chapter 4 Biaryls, pp. 83-154; b) Yuan, S.; Chang, J.; Yu, B. *Top. Curr. Chem.* **2020**, *378*, 23; c) Simonetti, M.; Cannas, D. M.; Larrosa, I. Chapter Four - Biaryl Synthesis *via* C–H Bond Activation: Strategies and Methods, *Adv. Organomet. Chem.* **2017**, *67*, 299; d) Willemse, T.;

Schepens, W.; Van Vlijmen, H. W. T.; Maes, B. U. W.; Ballet, S. *Catalysts* **2017**, *7*, 74; e) Kozlowski, M. C.; Morgan, B. J.; Linton, E. C. *Chem. Soc. Rev.* **2009**, *38*, 3193; f) Feliu, L.; Planas, M. *Int. J. Pept. Res. Ther.* **2005**, *11*, 53; g) Brown, D. G.; Boström, J. *J. Med. Chem.* **2016**, *59*, 4443; h) Xu, S. Kim, E. H.; Wei, A.; Negishi, E.-I. *Sci. Technol. Adv. Mater.* **2014**, *15*, 044201; i) Amna, B.; Siddiqui, H. M.; Hassan, A.; Ozturk, T. *RSC Adv.* **2020**, *10*, 4322; j) Kaya, K.; Yagci, Y. *Macromol. Chem. Phys.* **2021**, *222*, 2100334; k) Schiedel, M.-S.; Briehn, C. A.; Bäuerle, P. *J. Organomet. Chem.* **2002**, *653*, 200.

3. For selected reviews on polyaryls (polyphenylenes): a) Shi, W.; Yu, T.; Cui, D. *Chin. J. Org. Chem.* **2015**, *35*, 362; b) Snieckus, V. *Chem. Rev.* **1990**, *90*, 879; c) Liu, J.-K. *Chem. Rev.* **2006**, *106*, 2209; c) Li, W.; Li, X.-B.; Lou, H.-X. *J. Asian Nat. Prod. Res.* **2018**, *20*, 1; d) Jin, T.; Terada, M. *Tetrahedron* **2020**, *61*, 151514; e) Kotha, S.; Meshram, M.; Panguluri, N. R.; Shah, V. R.; Todeti, S.; Shirbhate, M. E. *Chem. Asian J.* **2019**, *14*, 1356; f) Moberg, C. *Angew. Chem. Int. Ed.* **1998**, *37*, 248; g) Vishnoi, P.; Kaleeswaran, D.; Murugavel, R. *RSC Adv.* **2018**, *8*, 17535; h) Kotha, S.; Lahiri, K. *Eur. J. Org. Chem.* **2007**, 1221; i) Wang, C.; Dong, H.; Hu, W.; Liu, Y.; Zhu, D. *Chem. Rev.* **2012**, *112*, 2208; j) Facchetti, A.; *Chem. Mater.* **2011**, *23*, 733.
4. For selected articles dealing with bioactive polyaryls, especially, terphenyls: a) Roberti, M.; Pzzirani, D.; Recanatini, M.; Simoni, D.; Grimaudo, S.; Cristina, A. D.; Abbadessa, V.; Gebbia, N.; Tolomeo, M. *J. Med. Chem.* **2006**, *49*, 3012; b) Yin, H.; Lee, G.I.; Park, H. S.; Payne, G. A.; Rodriguez, J. M.; Sebti, S. M.; Hamilton, A. D. *Angew. Chem. Int. Ed.* **2005**, *44*, 2704; c) Kutzki, O.; Park, H. S.; Ernst, J. T.; Omer, B. P.; Yin, H.; Hamilton, A. D. *J. Am. Chem. Soc.* **2002**, *124*, 11838; d) Medina-Trillo, C.; Sedgwick, D. M.; Herrera, L.; Beltrán, M.; Moreno, Á.; Barrio, P. ; Bedoya, L. M.; Alcami, J.; Fustero, S.; Gallego, J. *Sci. Rep.* **2020**, *10*, 7190; e) Kikuchi, H.; Matsuo, Y.; Katau, Y.; Kubohara, Y.; Oshima, Y. *Tetrahedron* **2012**, *68*, 8884; f) Chen, W.; Zhang, J.; Qi, X.; Zhao, K.; Pang, X.; Lin, X.; Liao, S.; Yang, B.; Zhou, X.; Liu, S.; Wang, J.; Yao, X.; Liu, Y. *J. Nat. Prod.* **2021**, *84*, 2822; g) Wang, S.-M.; Han, J.-J.; Ma, K.; Jin, T.; Bao, L.; Pei, Y.-F.; Liu, H.-W. *Fitoterapia* **2014**, *98*, 149; h) Muszak, D.; Surmiak, E.; Plewka, J.; Magiera-Mularz, J. K.; Kocik-Krol, B.; Musielak, D.; Sala, R.; Kitel, M.; Stec, K.; Weglarczyk, M.; Siedlar, A.; Dömling, L.; Skalniak, T.; Holak, A. *J. Med. Chem.* **2021**, *64*, 11614; i) Look, G. C.; Vacin, C.; Dias, T. M.; Ho, S.; Tran, T. H.; Lee, L. L.; Wiesner, C.; Fang, F.; Marra, A.; Westmacott, D.; Hromockyj, A. E.; Murphy, M. M.; Schullek, J. R. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 1423.

5. For selected articles dealing with polyaryls (polyphenylenes) in functional materials: a) Sasabe, H.; Seino, Y.; Kimura, M.; Kido, J. *Chem. Mater.* **2012**, *24*, 1404; b) Wu, C.-A.; Chou, H.-H.; Shih, C.-H.; Wu, F.-I.; Cheng, C.-H.; Huang, H.-L.; Chao, T.-C.; Tseng, M.-R. *J. Mater. Chem.* **2012**, *22*, 17792; c) Fan, L.; Zhang, Y.; Wang, J.; Zhao, L.; Wang, X.; Hu, T.; Zhang, X. *J. Solid State Chem.* **2018**, *260*, 46; d) Zhang, Y.; Han, J.; Liu, Z.-J.; *J. Org. Chem.* **2016**, *81*, 1317; e) Lee, C. W.; Lee, J. Y. *Org. Electron.* **2014**, *15*, 399; f) Duan, Y.; Xu, X.; Yan, H.; Su, W.; Li, Z.; Peng, Q. *Adv. Mater.* **2017**, *29*, 1605115; g) Ponomarenko, S. A.; Kirchmeyer, S.; Elschner, A.; Huisman, B.-H.; Karbach, A.; Drechsler, D. *Adv. Funct. Mater.* **2003**, *13*, 591; h) Cremer, J.; Bäuerle, P. *J. Mater. Chem.* **2006**, *16*, 874; i) Okumoto, K.; Shirota, Y. *Chem. Mater.* **2003**, *15*, 699; j) Kukhta, N. A.; Volyniuk, D.; Peciulyte, L.; Ostrauskaite, J.; Juska, G.; Grazulevicius, J. V. *Dyes Pigments* **2015**, *117*, 122; k) Weber, E.; Hecker, M.; Koepp, E.; Orlia, W.; Czugler, M.; Csöregh, I. *J. Chem. Soc. Perkin Trans. II* **1988**, 1251.
6. For selected papers on the synthesis of polyaryls (polyphenylenes) *via* classical routes: a) Saednya, A.; Hart, H. *Synthesis* **1996**, 1455; b) Liu, L.; Zhang, Y.; Xin, B. *J. Org. Chem.* **2006**, *71*, 3994; c) Paul, S.; Clark, J. H. *Green Chem.* **2003**, *5*, 635; d) Borhade, S. R.; Waghmode, S. B. *Beilstein J. Org. Chem.* **2011**, *7*, 310; e) Yu, D.-G.; Yu, M.; Guan, B.-T.; Li, B.-J.; Zheng, Y.; Wu, Z.-H.; Shi, Z.-J. *Org. Lett.* **2009**, *11*, 3374; f) Zhao, Y.; Snieckus, V. *J. Am. Chem. Soc.* **2014**, *136*, 11224; g) Chatelain, P.; Sau, A.; Rowley, C. N.; Moran, J. *Angew. Chem. Int. Ed.* **2019**, *58*, 14959; h) Organ, M. G.; Abdel-Hadi, M.; Avola, S.; Hadei, N.; Nasielski, J.; O'Brien, C. J.; Valente, C. *Chem. Eur. J.* **2007**, 13, 150; i) Vajpayee, V.; Song, Y. H.; Ahn, J. S.; Chi, K.-W. *Bull. Korean Chem. Soc.* **2011**, *32*, 2970; j) Kazi, S. A.; Campi, E. M.; Hearn, M. T. W. *Tetrahedron* **2017**, *74*, 1731; k) Jimenez, L. B.; Torres, N. V.; Borioni, J. L.; Pierini, A. B. *Tetrahedron* **2014**, *70*, 3614; l) Kotha, S.; Chakraborty, K.; Brahmachary, E. *Synlett* **1999**, 1621; m) Rajwar, D.; Sun, X.; Cho, S. J.; Grimsdale, A. C.; Fichou, D. *CrystEngComm* **2012**, *14*, 5182; n) Trawny, D.; Vandromme, L.; Rabe, J. P.; Reissig, H.-U. *Eur. J. Org. Chem.* **2014**, 4985.
7. Selected reviews on C-H functionalization: a) Kakiuchi, F.; Murai, S. *Acc. Chem. Res.* **2002**, *35*, 826; b) Rej, S.; Das, A.; Chatani, N. *Coord. Chem. Rev.* **2021**, *431*, 213683; c) Miura, M.; Satoh, T.; Hirano, K. *Bull. Chem. Soc. Jpn.* **2014**, *87*, 751; d) Lyons, T. W.; Sanford, M. S. *Chem. Rev.* **2010**, *110*, 1147; e) He, J.; Wasa, M.; Chan, K. S. L.; Shao, Q.; Yu, J.-Y. *Chem. Rev.* **2017**, *117*, 8754; f) Lu, M.-Z.; Goh, J.; Maraswami, M.; Jia, Z.; Tian, J.-S.; Loh, T.-P. *Chem. Rev.* **2022**, *122*, 17479; g) Yanagi, T.; Nogi, K.; Yorimitsu, H. *Tetrahedron Lett.* **2018**, *59*, 2951; h) Sinha, S. K.; Guin, S.; Maiti, S.; Biswas, J. P.; Porey,

S.; Maiti, D. *Chem. Rev.* **2022**, *122*, 5682; i) Manoharan, R.; Jeganmohan, M. *Asian J. Org. Chem.* **2019**, *8*, 1949; j) Mc Murray, L.; O'hara, F.; Gaunt, M. J. *Chem. Soc. Rev.* **2011**, *40*, 1885; k) Li, B.; Dixneuf, P. H. *Chem. Soc. Rev.* **2013**, *42*, 5744; l) Docherty, J. H.; Lister, T. M.; Mcarthur, G.; Findlay, M. T.; Domingo-Legarda, P.; Kenyon, J.; Choudhary, S.; Larrosa, I. *Chem. Rev.* **2023**, *123*, 7692; m) Motati, D. R.; Uredi, D.; Watkins, E. B.; *Stud. Nat. Prod. Chem.* **2019**, *63*, 81; n) Zhang, Q.; Liu, C.-F.; Chen, J.; Rao, G.-W. *Adv. Synth. Catal.* **2020**, *362*, 1406.

8. Selected reviews on bidentate directing group-aided C-H functionalization: a) Rej, S.; Ano, Y.; Chatani, N. *Chem. Rev.* **2020**, *120*, 1788; b) Daugulis, O.; Roane, J.; Tran, L. D. *Acc. Chem. Res.* **2015**, *48*, 1053; c) Sambiagio, C.; Schönbauer, D.; Blieck, R.; Dao-Huy, T.; Pototschnig, G.; Schaaf, P.; Wiesinger, T.; Zia, M. F.; Wencel-Delord, J.; Besset, T.; Maes, B. U. W.; Schnürch, M. *Chem. Soc. Rev.* **2018**, *47*, 6603; d) Liu, B.; Romine, A. M.; Rubel, C. Z.; Engle, K. M.; Shi, B.-F. *Chem. Rev.* **2021**, *121*, 14957; e) Rit, R. K.; Yadav, M. R.; Ghosh, K.; Sahoo, A. K. *Tetrahedron* **2015**, *71*, 4450; f) He, G.; Wang, B.; Nack, W. A.; Chen, G. *Acc. Chem. Res.* **2016**, *49*, 635; g) Babu, S. A.; Aggarwal, Y.; Patel, P.; Tomar, R. *Chem. Commun.* **2022**, *58*, 2612.
9. Selected articles on bidentate directing group-aided C-H functionalization: a) Shabashov, D.; Daugulis, O. *J. Am. Chem. Soc.* **2010**, *132*, 3965; b) Hasegawa, N.; Charra, V.; Inoue, S.; Fukumoto, Y.; Chatani, N.; *J. Am. Chem. Soc.* **2011**, *133*, 8070; c) Wang, Z.; Kuninobu, Y.; Kanai, M. *Org. Lett.* **2014**, *16*, 4790; d) Santrač, D.; Cella, S.; Wang, W.; Ackermann, L. *Eur. J. Org. Chem.* **2016**, 5429; e) Liu, Y.; Zhang, Y.; Wan, J.-P. *J. Org. Chem.* **2017**, *82*, 8950; f) Han, J.; Liu, P.; Wang, C.; Wang, Q.; Zhang, J.; Zhao, Y.; Shi, D.; Huang, Z.; Zhao, Y. *Org. Lett.* **2014**, *16*, 5682; g) Bolsakova, J.; Lukasevics, L.; Grigorgeva, L. *J. Org. Chem.* **2020**, *85*, 4482; h) Verma, A.; Elias, A. J. *Chem. Asian J.* **2023**, *18*, e202300191; i) Dutta, A.; Jeganmohan, M. *J. Org. Chem.* **2022**, *87*, 13154; j) Takamatsu, K.; Hayashi, Y.; Kawauchi, S.; Hirano, K.; Miura, M. *ACS Catal.* **2019**, *9*, 5336; k) Zhao, Q.; Poisson, T.; Pannecoucke, X.; Bouillon, J.-P.; Besset, T. *Org. Lett.* **2017**, *19*, 5106; l) Sattar, M.; Praveen.; Prasad, C. D.; Verma, A.; Kumar, S.; Kumar, S. *Adv. Synth. Catal.* **2016**, *358*, 240; m) Cheng, X.; Chen, Z.; Gao, Y.; Xue, F.; Jiang, C. *J. Org. Chem.* **2016**, *14*, 3298; n) Reddy, V. P.; Qiu, R.; Iwasaki, T.; Kambe, N. *Org. Biomol. Chem.* **2015**, *13*, 6803.
10. Selected articles from our group dealing with directing group-aided C-H functionalization: a) Parella, R.; Babu, S. A. *J. Org. Chem.* **2017**, *82*, 7123; b) Reddy, C.; Bisht, N.; Parella, R.; Babu, S. A. *J. Org. Chem.* **2016**, 81, 12143; c) Parella, R.; Babu, S. A. *J. Org. Chem.*

2015, *80*, 2339; d) Naveen.; Rajkumar, V.; Babu, S. A.; Gopalakrishnan, B. *J. Org. Chem.* **2016**, *81*, 12197; e) Bisht, N.; Babu, S. A. *Tetrahedron* **2016**, 72, 5886; f) Dalal, A.; Babu, S. A. *Synthesis* **2021**, *53*, 3307; g) Bisht, N.; Singh, P.; Babu, S. A. *Synthesis* **2022**, *54*, 4059; h) Singh, P.; Babu, S. A.; Aggarwal, Y.; Patel, P. *Asian J. Org. Chem.* **2021**, 10, 180; i) Tomar, R.; Kumar, A.; Dalal, A.; Bhattacharya, D.; Singh, P.; Babu, S. A. *Asian J. Org. Chem.* **2022**, 11, e202200311; j) Padmavathi, R.; Sankar, R.; Gopalakrishnan, B.; Babu, S. A. *Eur. J. Org. Chem.* **2015**, 3727; k) Padmavathi, R.; Babu, S. A. *Org. Biomol. Chem.* **2023**, *21*, 2689; l) Banga, S.; Kaur, R.; Babu, S. A. *Eur. J. Org. Chem.* **2021**, 3641; m) Bisht, N.; Babu, S. A.; Tomar, R. *Asian J. Org. Chem.* **2020**, *9*, 1225; n) Singh, P.; Babu, S. A. *Eur J. Org. Chem.* **2023**, *26*, e202300440; o) Bisht, N.; Babu, S. A.; Tomar, R. *Asian J. Org. Chem.* **2022**, *11*, e202200589; p) Tomar, R.; Suwasia, S.; Roychoudhury, A.; Venkataramani, S.; Babu, S. A. *Chem. Commun.* **2022**, *58*, 12967; q) Kaur, R.; Banga, S.; Babu, S. A. *Org. Biomol. Chem.* **2022**, *20*, 4391.

11. Selected reviews dealing with C-H functionalization of biaryls: a) Wang, J.; Liu, C.-F.; Zheng, Q.; Rao, G.-W. *Eur. J. Org. Chem.* **2020**, 3737; b) Simonetti, M.; Cannas, D. M.; Larrosa, I. Chapter Four - Biaryl Synthesis *via* C–H Bond Activation: Strategies and Methods, *Adv. Organomet. Chem.* **2017**, *67*, 299; c) Zhang, Y. F.; Shi, Z.-J. *Acc. Chem. Res.* **2019**, *52*, 161; d) Felpin, F.-X.; Sengupta, S. *Chem. Soc. Rev.* **2019**, *48*, 1150.
12. Selected reviews on C-H functionalization route to π-conjugated molecules or extended π-systems: a) Okamoto, K.; Zhang, J.; Housekeeper, J. B.; Marder, S. R.; Luscombe, C. K. *Macromolecules* **2013**, *46*, 8059; b) Zhang, J.; Kang, L. J.; Parker, T. C.; Blakey, S. B.; Luscombe, C. K.; Marder, S. R. *Molecules* **2018**, *23*, 922; c) Segawa, Y.; Maekawa, T.; Itami, K. *Angew. Chem. Int. Ed.* **2015**, *54*, 66; d) Alberico, D.; Scott, M. E.; Lautens, M. *Chem. Rev.* **2007**, *107*, 174; e) Chen, X.; Engle, K. M.; Wang, D.-H.; Yu, J.-Q. *Angew. Chem. Int. Ed.* **2008**, *48*, 5094; f) Ackermann, L.; Vicente, R.; Kapdi, A. R. *Angew. Chem. Int. Ed.* **2009**, *48*, 9792.
13. Selected articles on the C-H functionalization route to π-conjugated molecules (polyaryls): a) Feng, R.; Gao, Y.; Liu, Z.; Zhang, Y. *Synlett* **2017**, *28*, 2147; b) Dyadyuk, A.; Sudheendran, K.; Vainer, Y.; Vershinin, V.; Shames, A. I.; Pappo, D. *Org. Lett.* **2016**, *18*, 4324; c) Truong, T.; Mesgar, M.; Le, K. K. A.; Daugulis, O. *J. Am. Chem. Soc.* **2014**, *136*, 8568; d) Jiang, H.; Zhang, Y.; Chen, D.; Zhou, B.; Zhang, Y. *Org. Lett.* **2016**, *18*, 2032; e) Dherbassy, Q.; Wencel-Delord, J.; Colobert, F. *Tetrahedron* **2018**, *74*, 6205; f) Feng, J.; Lu, G.; Lv, M.; Cai, C. *Synlett* **2013**, *24*, 2153.

14. Selected articles dealing with the synthesis of π-extended biaryls *via* C-H functionalization involving biaryl type coupling partners: a) Li, W.; Yin, Z.; Jiang, X.; Sun, P. *J. Org. Chem.* **2011**, *76*, 8543. b) Maiti, S.; Li, Y.; Sasmal, S.; Guin, S.; Bhattacharya, T.; Lahiri, G. K.; Paton, R. S.; Maiti, D. *Nat. Commun.* **2022**, *13*, 3963. c) Dutta, U.; Porey, S.; Pimparkar, S.; Mandal, A.; Grover, J.; Koodan, A.; Maiti, D. *Angew. Chem. Int. Ed.* **2020**, *16*, 20831. d) Modak, A.; Rana, S.; Maiti, D. *J. Org. Chem.* **2015**, *80*, 296. e) Liang, Z.; Feng, R.; Yin, H.; Zhang, Y. *Org. Lett.* **2013**, *15*, 4544. f) Li, J.-W.; Wang, L.-N.; Li, M.; Tang, P.-T.; Luo, X.-P.; Kurmoo, M.; Liu, Y.-J.; Zheng. M.-H. *Org. Lett.* **2019**, *21*, 2885.
15. Articles dealing with C-H functionalization using biaryl-based carboxamides: a) Du, C.; Li, P.-X.; Zhu, X.; Han, J.-N.; Niu, J.-L.; Song, M.-P. *ACS Catal.* **2017**, *7*, 2810; b) Sunnam, S. K.; Belani, J. D.; *Chem. Eur. J.* **2021**, *27*, 8846; c) Bu, Q.; Gońka, E.; Kuciński, K.; Ackermann, L.; *Chem. Eur. J.* **2019**, *25*, 2213; d) Yokota, A.; Aihara, Y.; Chatani, N.; **2014**, *79*, 11922; e) Aihara, Y.; N. Chatani, **2014**, *4*, 664; f) Castro, L. C. M.; Obata, A.; Aihara, Y.; Chatani, N. *Chem. Eur. J.* **2016**, *22*, 1362; g) He, Z.; Huang, Y. *ACS Catal.* **2016**, *6*, 7814; h) Manoharan, R.; Jeganmohan, M. *Org. Biomol. Chem.* **2018**, *16*, 8384; i) Suwasia, S.; Venkataramani, S.; Babu, S. A. *Org. Biomol. Chem.* **2023**, *21*, 1793; j) Zhang, T-Y.; Lin, J.-B.; Li, Q.-Z.; Kang, J.-C.; Pan, J.-L.; Hou, S.-H.; Chen, C.; Zhang, S.-Y.; *Org. Lett.* **2017**, *19*, 1764.
16. UV-Vis absorption (λ_{max} (nm)) value for compounds, (nm) **5a**: (261), **5aa**: (262), **5ab**: (270), **5ac**: (291), **5ad**: (259), **5ae**: (259), **5af**: (266), **5ag**: (266), **5ah**: (271), **5ai**: (270), **5aj** (262), **5ak**: (265), **6a**: (262), **6b**: (261), **6c**: (269), **6d**: (269), **6e**: (262), **6f**: (269), **6g**: (262), **6h**: (277), **6i**: (284), **6j**: (245), **6k**: (245), **6l**: (295), **6m**: (264), **6n**: (288), **6o**: (268), **5al**: (259), **5am**: (263), **5an**: (262), **5ao**: (260), **5ap**: (262), **5aq**: (261), **5ar**: (266), **12a**: (265), **12b**: (266), **12c**: (266), **12d**: (246), **12e**: (258), **12f**: (267), **13a**: (273), **13b**: (278), **13c**: (276), **13d**: (284), **13e**: (284), **13f**: (273), **13g**: (273), **13h**: (284), **13i**: (278), **13j**: (286), **13k**: (284), **15a**: (264), **15b**: (269), **15b**-(R): (269), **15b**-(S): (269), **15c**: (269), **15c**-(R): (269), **15c**-(S): (269), **15d**: (263), **15d**-(R): (263), **15d**-(S): (263), **17a**: (292), **17b**: (291), **17c**: (293), **17d**: (294), **18a**: (259), **18b**: (253), **18c**: (267), **18d**: (285), **18e**: (284), **19**: (293), **20a**: (264), **22**: (268), **21**-(DL): (265), **21**-(L): (265), **23**-(DL): (268); **23**-(D): (267), **23**-(L): (267), **24**-(DL): (267); **24**-(L): (266), **25**: (266).
17. CCDC 2294228 (**6n**) and CCDC 2294229 (**18a**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* www.ccdc.cam.ac.uk/data_request/cif.

Chapter 4

Pd(II)-catalyzed C-H arylation and alkylation of pyrene core using 8-aminoquinoline and 2-picolinic acid as directing groups.

For the purpose of this Thesis work, the work of Chapter 4 is re-used (adapted) with permission from Dalal, A.; Babu, S. A*. *Synthesis* **2021**, *53*, pp 3307-3324. (Title; Pd(II)-catalyzed directing group-aided C-H arylation and alkylation of pyrene core. Synthesis of C1,C2- and C1,C10-disubstituted pyrene motifs).

During the era when the cross-coupling reaction was chronically practiced in organic synthesis,[1,2] there were some pioneering efforts of direct functionalization of C-H bonds in small organic molecules to achieve the C-C bond construction. In 1955 and 1956 Murahashi reported[3] the cobalt-promoted insertion of carbon monoxide into an *ortho*-C(sp^2)-H bond of aldimine and azobenzene substrates. Subsequently, various stoichiometric metal-promoted C–H bond activation reactions involving cyclometallated species were published.[4] In 1970, the palladium-catalyzed chlorination of an *ortho*-C(sp^2)-H bond of azobenzene reported by Fahey is another important discovery.[5] Successively, Jordan (1989), Moore (1992) and Murai (1993) reported the breakthrough catalytic C-H activation/functionalization methods involving Zr- and Ru-based catalysts.[6-8] During the last 20 years, the research area pertaining to the transition metal-catalyzed C-H bond activation reactions have advanced at a rapid phase.[9-11]

Pertinently, the transition metal-catalyzed sp^2/sp^3 C-H activation/functionalization considered to be a remarkable synthetic strategy to functionalize small organic molecules. The catalytic C-H functionalization of sp^2/sp^3 C-H bonds of small organic molecules have been accomplished with or without the help of a directing group.[9-15] In particular, the directing group-aided sp^2 and sp^3 C-H activation/functionalization strategy has received significant attention in organic synthesis. This is because, the directing group-aided C-H activation/functionalization strategy offers the feasibility to functionalize the required substrates with site-selectivity or regioselectivity as well as stereoselectivity. Along this line, the Pd(II)-catalyzed bidentate directing group (BDG)-aided site-selective sp^2 and sp^3 C-H activation/functionalization of carboxamides are considered as benchmark strategies.[11-15] The site-selective C-H functionalization of carboxamides derived from carboxylic acid substrates were achieved with the help of 8-aminoquinoline type BDGs (introduced by Daugulis).[11-15] On

the other hand, the site-selective C-H functionalization of carboxamides derived from amine substrates were achieved with the help of picolinamide type BDGs.[11-15]

Due to the superior fluorescence properties, efficient excimer emission, high charge carrier mobility, pyrene and its derivatives have received much attention in various fields of chemical sciences including organic-, supramolecular and materials chemistry.[16-19] Markedly, pyrenes are important building blocks to assemble materials such as organic light-emitting diodes (OLEDs), organic semiconducting materials for OFETs, supramolecular sensors, solar cells etc. Almost all types of photoelectric devices have been investigated using various pyrene-based organic materials.[16b-d,18] It is documented that the opto-electronic and photophysical properties of pyrenes are strongly dependent on the respective substituents and their positions.[16,17,19] Consequently, several methodologies have been developed to functionalize the multi reactive positions of pyrene core.[16,17]

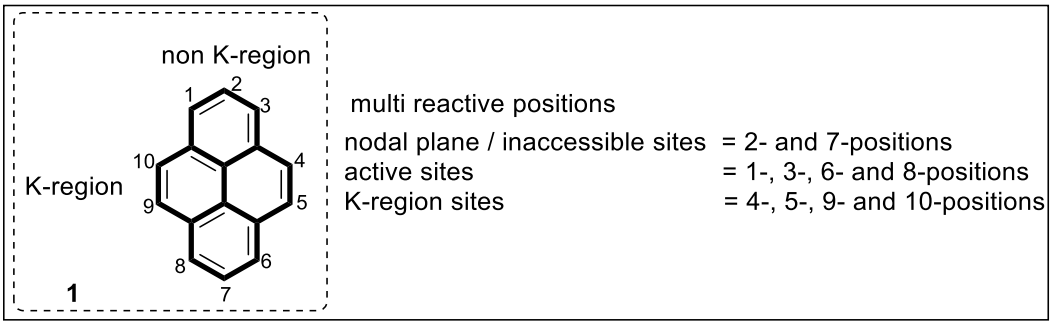
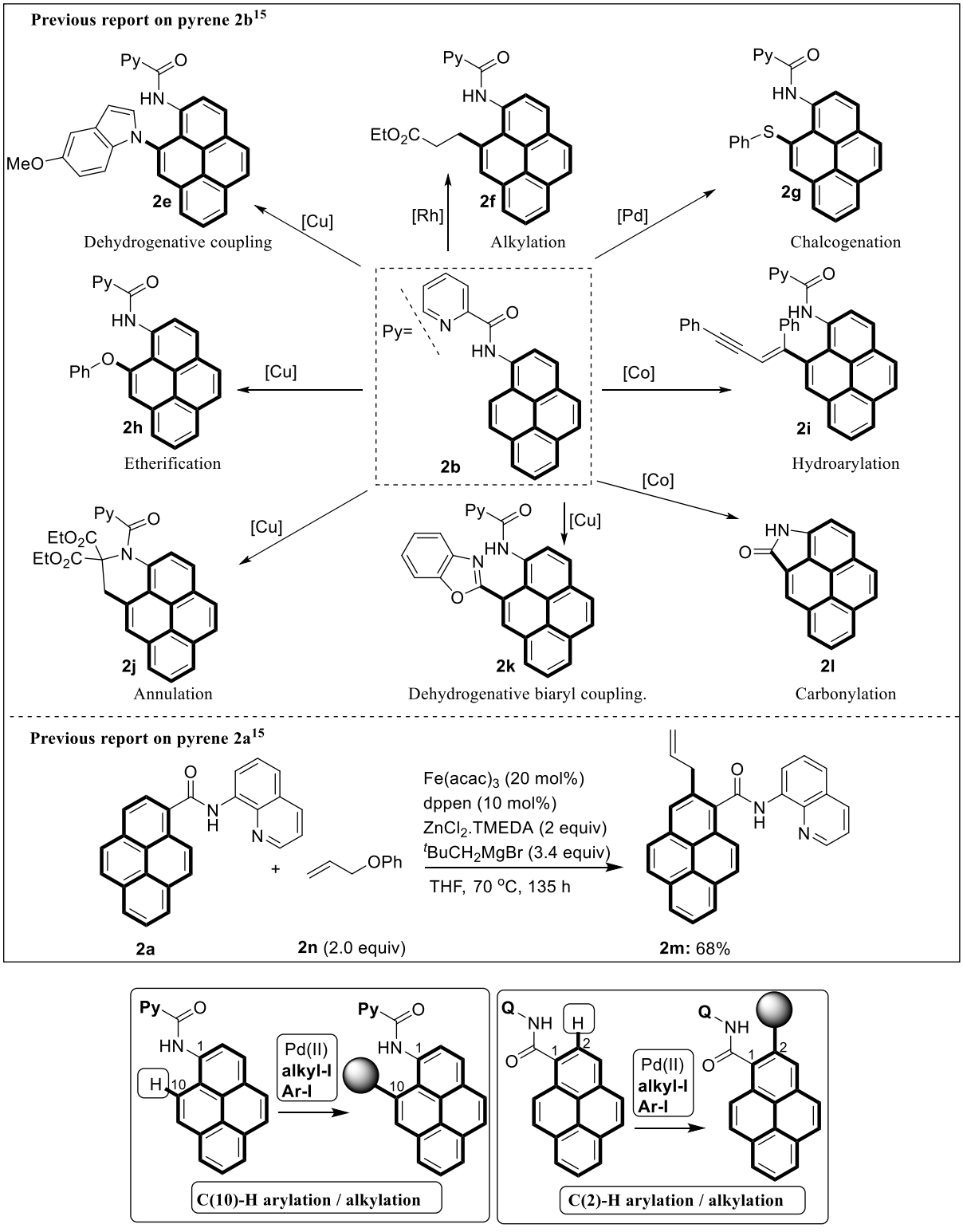


Figure 1. K-region and non K-region of pyrene motif.

The 1-, 3-, 6- and 8-positions of pyrene are known as 'active/common sites' and these sites have rich electron density and readily undergo electrophilic aromatic substitution (S_EAr) reactions.[16b] Generally, pyrene derivatives have been synthesized by introducing substitutions at these active/common sites. The 2- and 7-positions of pyrene are known as 'nodal plane positions and uncommon or inaccessible sites' and relatively difficult to functionalize (figure 1).[16b] It may be noted that the Friedel-Crafts *tert*-butylation and Ir-catalyzed direct borylation reactions have been carried out at these positions. The 4-, 5-, 9- and 10-positions of pyrene are known as 'the K-region sites' and it may be noted that oxidation and Pd-catalyzed oxidative direct arylation reactions have been carried out at these positions and these results have been summarized by Feng and Yamato.[16b]



Scheme 1. Previous report and theme of this work. C-H Arylation/alkylation of pyrene amide motifs.

Admired by the chemical transformations carried out on pyrene core and importance of the pyrene derivatives in chemical sciences,[15-19] we intended in taking forward the functionalization of pyrene core through the directing group-aided C-H functionalization route to assemble some new pyrene amide motifs. A few instances of functionalization of pyrene

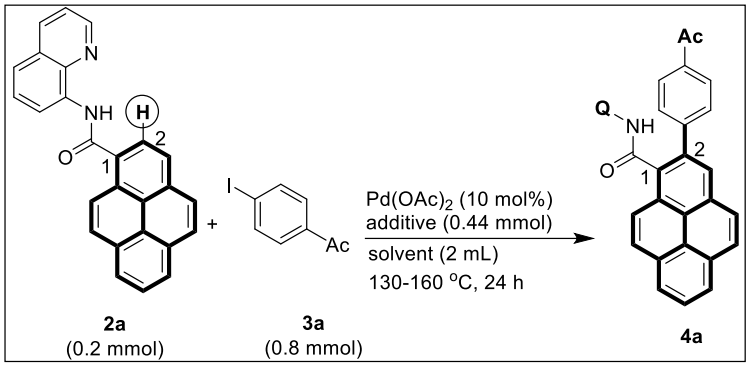
core through the directing group-aided C-H functionalization is known in the literature. Nevertheless, the available reports revealed single examples of functionalization of pyrene core (Scheme 1).[15] We envisaged to contribute to the existing developments by performing the bidentate directing group-aided site-selective C-H arylation and alkylation of the relatively inaccessible C2 position and K-region C10 position of pyrene amides **2a** and **2b**, respectively. To the best of our knowledge, the bidentate directing group-aided site-selective C-H arylation and alkylation C2 position and C10 position of pyrene amides are not yet explored. In continuation of our interest on the C-H activation reactions, herein we report the pd(II)-catalyzed, directing group-aided arylation/alkylation of C(2)-H bond of pyrene-1-carboxamide motif **2a** linked with 8-aminoquinoline DG and C(10)-H bond of 1-aminopyrene motif **2b** linked with picolinamide DG and assembling of various C1,C2- and C1,C10-disubstituted pyrene amide motifs.

Results and Discussion:

To begin with the assembling of C1, C2- and C1, C10-disubstituted pyrene motifs *via* the Pd(II)-catalyzed, directing group-aided C-H arylation/alkylation reaction, initially we prepared the pyrene-1-carboxamide **2a** possessing 8-aminoquinoline directing group, which will enable the selective β-C(sp^2)-H functionalization of **2a** (C2-position, Table 1). We performed some optimization reactions by employing the standard Pd(II)-catalyzed sp^2 β-C-H arylation conditions.[11-13] Typically, the directing group 8-aminoquinoline-aided C-H functionalization of carboxamides have been carried out by using a Pd(II) catalyst and an additive such as, AgOAc or Ag_2CO_3 or K_2CO_3 etc, and the additive will function as a halide ion scavenger.[11-13]

At first, we heated a mixture of pyrene-1-carboxamide **2a**, ArI (**3a**) and $Pd(OAc)_2$ catalyst (10 mol%) in the presence of Ag_2CO_3 as an additive in *o*-xylene at 135 ^oC for 24 h and this reaction yielded the C(2)-H arylated pyrene-1-carboxamide **4a** in satisfactory yield (38%, entry 1, Table 1). Next, the same reaction was carried out in the presence of Cs_2CO_3 as an additive instead of Ag_2CO_3 and this reaction also yielded the C(2)-H arylated pyrene-1-carboxamide **4a** in satisfactory yield (40%, entry 2, Table 1).

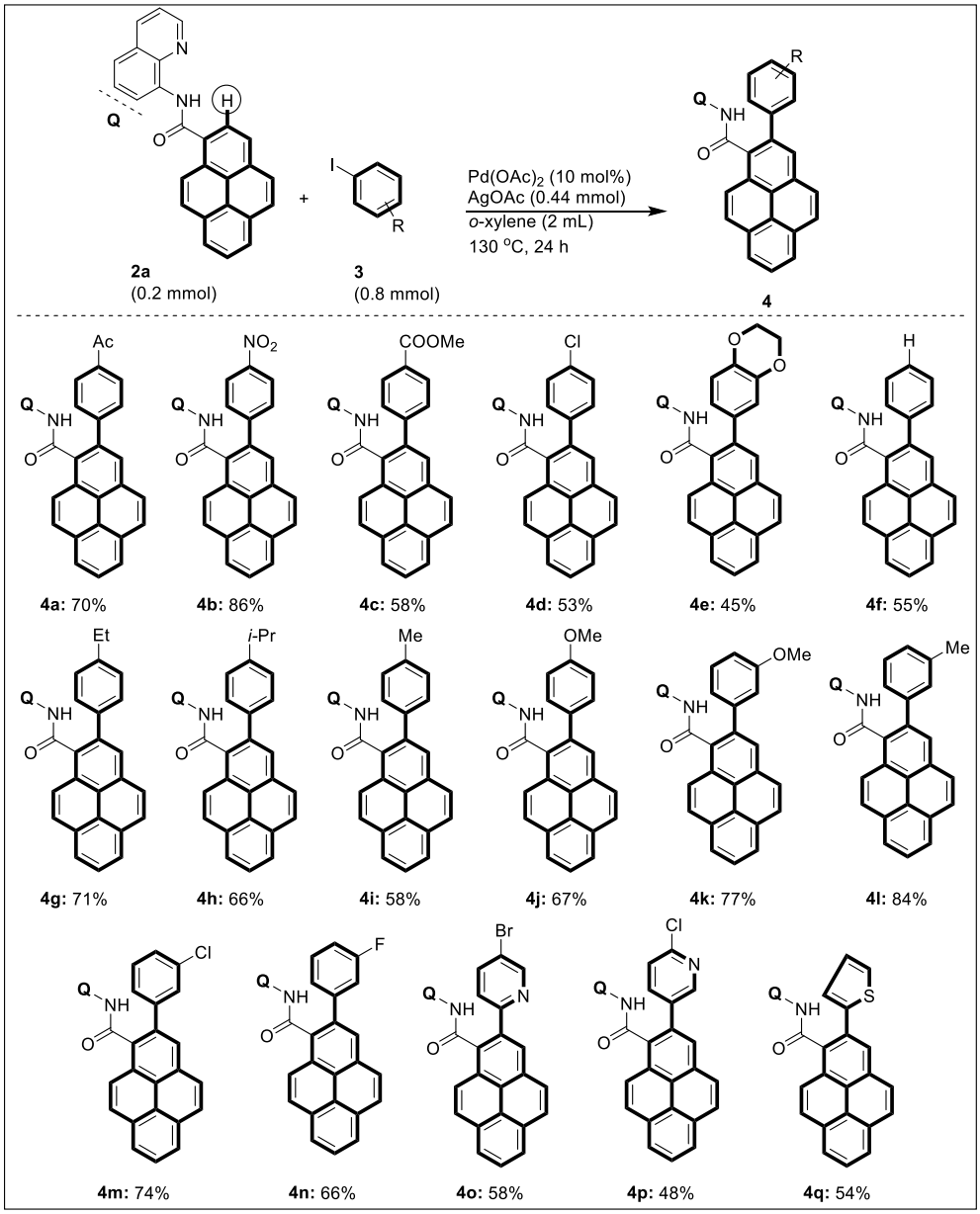
Table 1. Optimization reactions. C-H Arylation of pyrene carboxamide **2a** and assembling of C1,C2-disubstituted pyrene motif **4a.**



entry	catalyst	Additive	solvent	*T* °C	**4a**: Yield (%)
1	$Pd(OAc)_2$	Ag_2CO_3	*o*-xylene	135	38
2	$Pd(OAc)_2$	Cs_2CO_3	*o*-xylene	135	40
3	$Pd(OAc)_2$	K_2CO_3	*o*-xylene	135	51
4	**$Pd(OAc)_2$**	**AgOAc**	***o*-xylene**	**135**	**70**
5	$Pd(OAc)_2$	AgOAc	1,2-DCE	130	65
6[a]	$Pd(OAc)_2$	AgOAc	*o*-xylene	130	22
7[b]	$Pd(OAc)_2$	AgOAc	*o*-xylene	130	35
8[c]	$Pd(OAc)_2$	AgOAc	*o*-xylene	130	47
9	$Pd(TFA)_2$	AgOAc	*o*-xylene	130	60
10	$Pd(CH_3CN)_2Cl_2$	AgOAc	*o*-xylene	130	53
11	$Ni(OTf)_2$	$NaHCO_3$	toluene	160	15

[a] 0.2 mmol of **3a**. [b] 0.4 mmol of **3a**. [c] 0.6 mmol of **3a**.

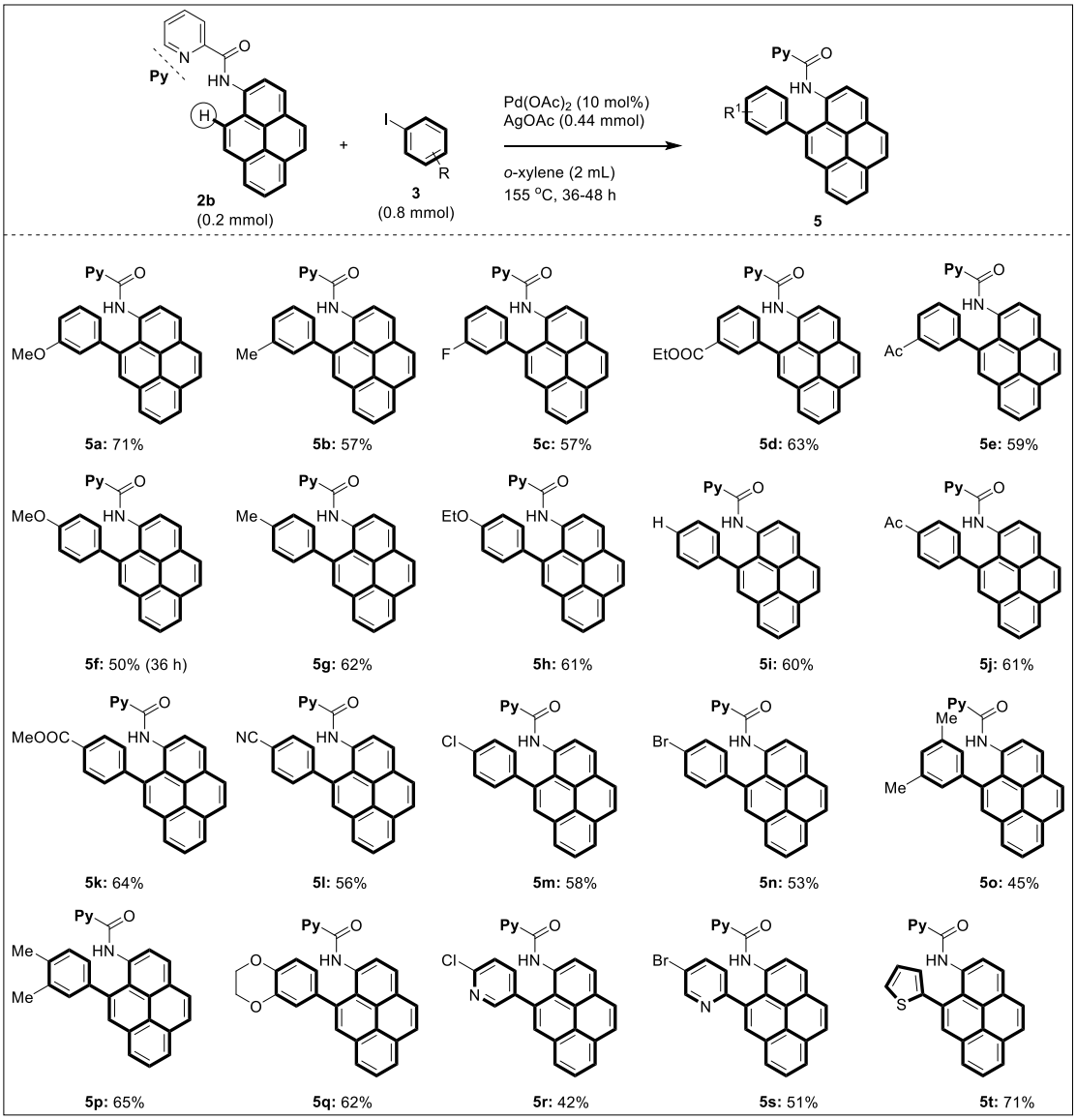
The Pd(II)-catalyzed arylation of pyrene-1-carboxamide **2a** by using K_2CO_3 as an additive yielded the C(2)-H arylated pyrene-1-carboxamide **4a** in an improved yield (51%, entry 3, Table 1). The Pd(II)-catalyzed arylation of pyrene-1-carboxamide **2a** in the presence of AgOAc as an additive in *o*-xylene or 1,2-DCE at 130-135 °C yielded the C(2)-H arylated pyrene-1-carboxamide **4a** in 65-70% yields (entries 4 and 5, Table 1). The Pd(II)-catalyzed arylation of pyrene-1-carboxamide **2a** by using different equiv of **3a** (1-3 equiv) yielded the product **4a** in 22-47% yields (entries 6-8, Table 1). The arylation of pyrene-1-carboxamide **2a** by using different palladium catalysts such as, $Pd(TFA)_2$ and $Pd(CH_3CN)_2Cl_2$ yielded the product **4a** in 53-60% yields (entries 9 and 10, Table 1). The C-H arylation of pyrene-1-carboxamide **2a** under the $Ni(OTf)_2$-catalyzed reaction conditions yielded the C(2)-H arylated pyrene-1-carboxamide **4a** in only 15% yield. (entry 11, Table 1)



Scheme 2. Assembling of C1,C2- disubstituted pyrene carboxamide motifs **4a-q** *via* the Pd(II)-catalyzed, 8-aminoquinoline-directed C-H arylation of **2a.**

Having the optimized reaction conditions in hand for the Pd(II)-catalyzed C(2)-H arylation of pyrene-1-carboxamide **2a**, we next intended to enrich the library of pyrene-1-carboxamide *via* the Pd(II)-catalyzed C(2)-H arylation reaction. Towards this, we carried out the Pd(II)-catalyzed C(2)-H arylation of pyrene-1-carboxamide **2a** using a variety of aryl iodides (Scheme 2). The Pd(II)-catalyzed C(2)-H arylation of pyrene-1-carboxamide **2a** with aryl iodides containing different electron-withdrawing substituents (e.g., Ac, NO_2, COOMe and Cl) at the *para* position yielded the corresponding C(2)-H arylated pyrene-1-carboxamides **4a-d** in moderate to good yields (53-86%, Scheme 2). Next, the Pd(II)-catalyzed C(2)-H arylation of pyrene-1-carboxamide **2a** with 6-iodo-2,3-dihydrobenzo[*b*][1,4]dioxine, PhI and aryl iodides

containing different electron-donating substituents (e.g., Et, *i*-Pr, Me and OMe) at the *para* position yielded the corresponding C(2)-H arylated pyrene-1-carboxamides **4e-j** in moderate to good yields (45-71%, Scheme 2).



Scheme 3. Assembling of C1,C10- disubstituted pyrene carboxamide motifs **5a-t** *via* the Pd(II)-catalyzed, picolinamide-directed C-H arylation of **2b.**

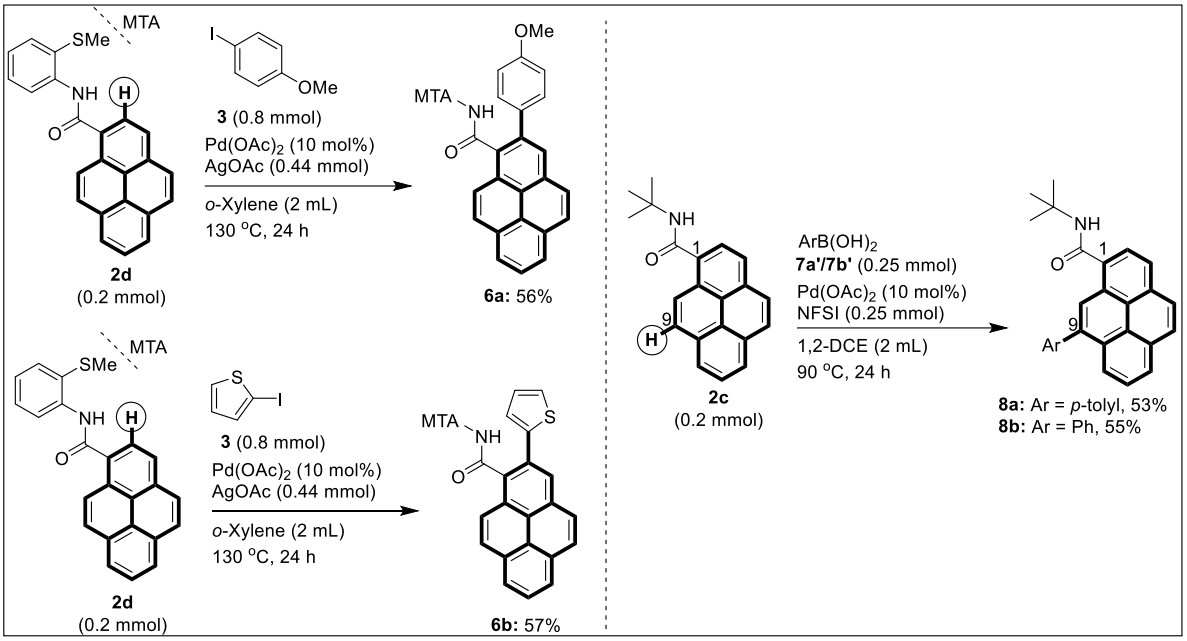
Then, we performed the Pd(II)-catalyzed C(2)-H arylation of pyrene-1-carboxamide **2a** with aryl iodides containing different electron-donating or electron-withdrawing substituents (e.g., OMe, Me, Cl and F) at the *meta* position, which yielded the corresponding C(2)-H arylated pyrene-1-carboxamides **4k-n** in 66-84% yields (Scheme 2). Furthermore, the Pd(II)-catalyzed C(2)-H arylation of pyrene-1-carboxamide **2a** with different heteroaryl iodides also yielded the corresponding C(2)-H arylated pyrene-1-carboxamides **4o-q** in satisfactory to moderate yields

(48-58%, Scheme 2). The structures of representative pyrene derivatives **4a**, and **4e** were confirmed by the X-ray structure analysis (Figure 2).

After assembling various C(2)-H arylated pyrene-1-carboxamides **4a-q**, we then planned to expand the scope of this work and enrich the library of 1-aminopyrene core by assembling various C(10)-H arylated 1-aminopyrene-based motifs (Schemes 3). Towards this, we prepared *N*-(pyren-1-yl)picolinamide (**2b**) possessing picolinamide directing group, which will enable the γ-C(sp^2)-H functionalization of **2b** at the C10-position. We then performed the Pd(II)-catalyzed C(10)-H arylation of *N*-(pyren-1-yl)picolinamide (**2b**) by using a variety of aryl iodides (Scheme 3). The Pd(II)-catalyzed C(10)-H arylation of *N*-(pyren-1-yl)picolinamide (**2b**) with aryl iodides containing different electron-donating or electron-withdrawing substituents (e.g., OMe, Me, F, COOEt and Ac) at the *meta* position yielded the corresponding C(10)-H arylated *N*-(pyren-1-yl)picolinamides **5a-e** in moderate to good yields (57-71%, Scheme 3).

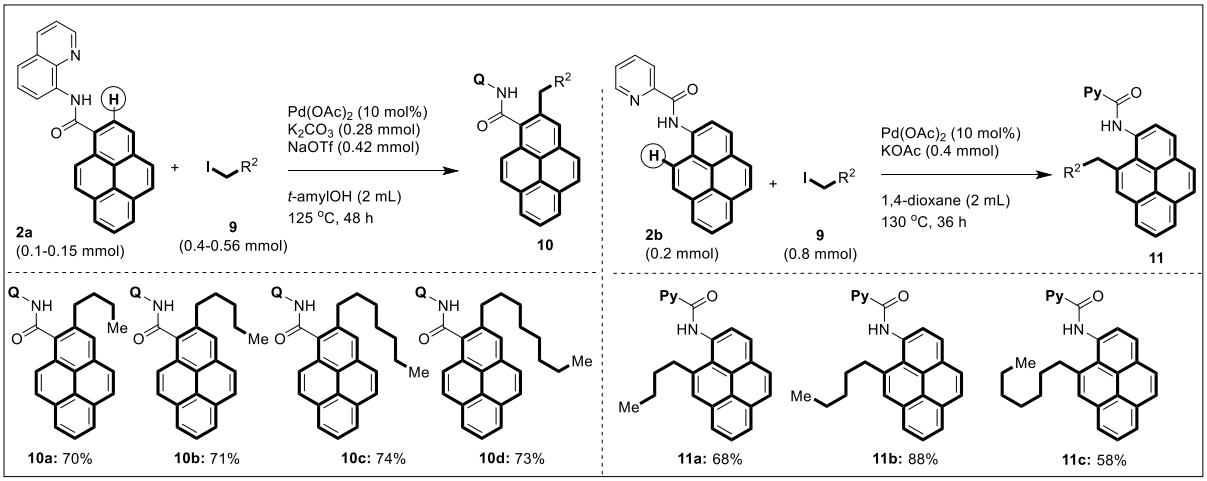
Next, the Pd(II)-catalyzed C(10)-H arylation of *N*-(pyren-1-yl)picolinamide (**2b**) with PhI and different aryl iodides containing different electron-donating and electron withdrawing substituents (e.g., OMe, Me, OEt, Ac, COOMe, CN, Cl and Br) at the *para* position yielded the corresponding C(10)-H arylated *N*-(pyren-1-yl)picolinamides **5f-n** in moderate to good yields (50-64%, Scheme 3). The Pd(II)-catalyzed C(10)-H arylation of *N*-(pyren-1-yl)picolinamide (**2b**) with disubstituted aryl iodides and 6-iodo-2,3-dihydrobenzo[*b*][1,4]dioxine yielded the corresponding C(10)-H arylated *N*-(pyren-1-yl)picolinamides **5o-q** in satisfactory to good yields (45-65%, Scheme 3). Furthermore, the C(10)-H arylation of *N*-(pyren-1-yl)picolinamide (**2b**) with different heteroaryl iodides also yielded the corresponding C(10)-H arylated *N*-(pyren-1-yl)picolinamides **5r-t** in satisfactory to good yields (42-71%, Scheme 3). The structures of representative pyrene carboxamide **5n** was confirmed by the X-ray structure analysis (Figure 2).

Next, we explored the possibility of using some other directing group similar to 8-aminoquinoline. Accordingly, we prepared the pyrene-1-carboxamides **2d** possessing 2-(methylthio)aniline as the directing group[11] (Scheme 4). We then performed the Pd(II)-catalyzed C(10)-H arylation of **2d** with different aryl iodides (Scheme 4), which also afforded the corresponding products **6a,b** in 56-57% yields.



Scheme 4. Assembling of pyrene carboxamide motifs **6a,b** and **8a,b** *via* the Pd(II)-catalyzed C-H arylation of **2c,d**.

Furthermore, we also attempted the functionalization of C9-position of pyrene core by using the procedure reported by Yang and You for the 1-naphthylamine system.[10m] In this regard, we treated the pyrene-1-carboxamide **2c** with *p*-tolylboronic acid and in the presence of the $Pd(OAc)_2$ catalyst and NFSI as an additive in 1,2,-DCE at 90 °C for 24 h, which afforded the corresponding C(9)-H arylated pyrene-1-carboxamide **8a** in 53% yield (Scheme 4). Similarly, the reaction of pyrene-1-carboxamide **2c** with phenylboronic acid in the presence of the $Pd(OAc)_2$ catalyst and NFSI as an additive in 1,2,-DCE at 90 °C for 24 h afforded the C(9)-H arylated pyrene-1-carboxamides **8b** in 55% yield (Scheme 4).



Scheme 5. Assembling of C1,C2- and C1,C10-disubstituted pyrene carboxamide motifs **10a-d** and **11a-c** *via* the C-H alkylation of pyrene core.

To further extend the substrate scope and enrich the library of pyrene-1-carboxamide and 1-aminopyrene core, we attempted the Pd(II)-catalyzed alkylation of C(2)-H and C(10)-H bonds of pyrene amides **2a** and **2b**, respectively. Towards this, we carried out the Pd(II)-catalyzed C(2)-H alkylation of pyrene-1-carboxamide **2a** with different alkyl iodides, which successfully yielded the corresponding C(2)-H alkylated pyrene-1-carboxamides **10a-d** in good yields (70-74%, Scheme 5). Similarly, the Pd(II)-catalyzed C(10)-H alkylation of *N*-(pyren-1-yl)picolinamide (**2b**) with different alkyl iodides yielded the corresponding C(10)-H alkylated *N*-(pyren-1-yl)picolinamide **11a-c** in good yields (68-88%, Scheme 5).

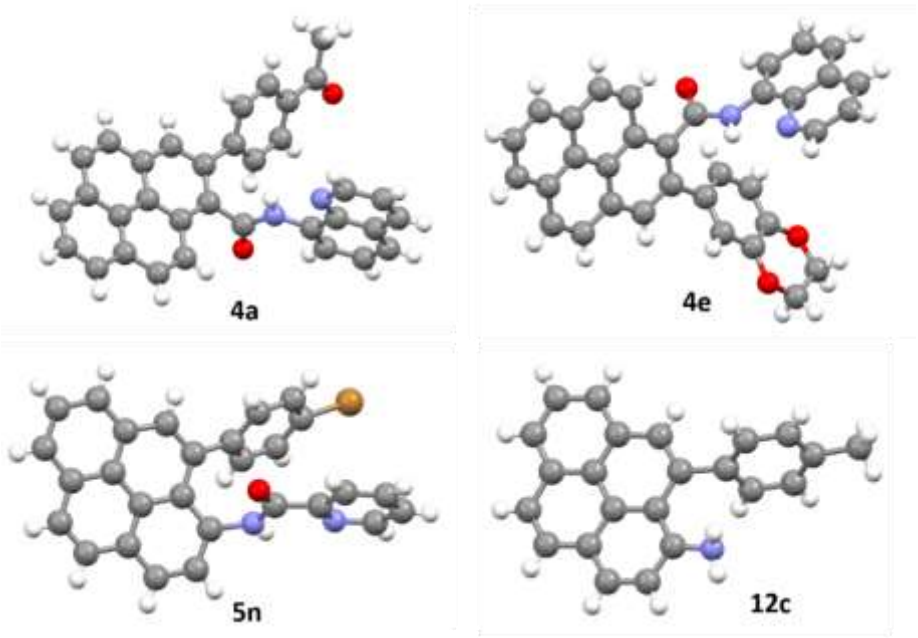
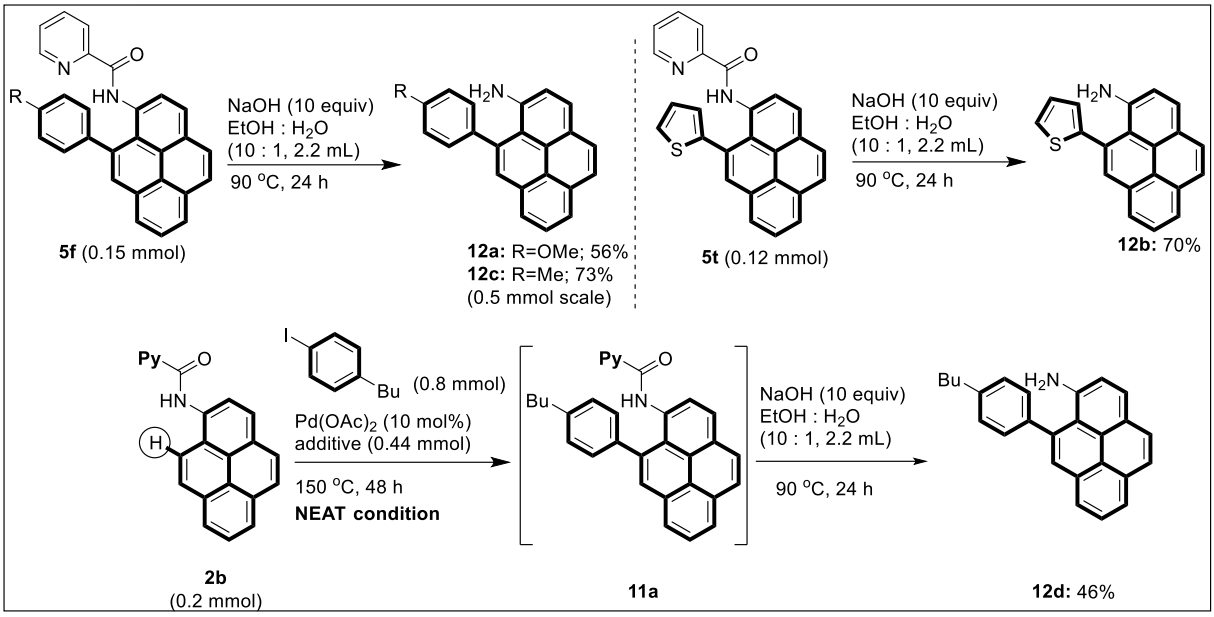


Figure 2. X-ray (ball and stick model) structures of compounds 4a, 4e, 5n and 12c.

We also attempted the removal of the directing group after the C-H arylation of the pyrene amides. In this regard, the C(10)-H arylated *N*-(pyren-1-yl)picolinamide **5f** was subjected to different amide hydrolysis conditions. Out of a few attempts carried out, we found that heating a mixture of *N*-(pyren-1-yl)picolinamide **5f** and NaOH in EtOH/H_2O at 90 ^oC for 24 h yielded the C(10)-H arylated 1-aminopyrene derivative **12a** in 56% yield (Scheme 6). Similarly, the NaOH-mediated hydrolysis of the C-H arylated *N*-(pyren-1-yl)picolinamides **5t,q** yielded the corresponding C(10)-H arylated 1-aminopyrene derivatives **12b,c** in 70-73% yields (Scheme 6). Finally, the compound **12d** was obtained *via* a one-pot sequential C-H arylation of **2b** under standard reaction conditions and neat condition followed by NaOH-mediated hydrolysis procedure (Scheme 6). The structures of representative pyrene derivative **12c** was unequivocally established by the X-ray structure analysis (Figure 2).[20]



Scheme 6. Trials on the removal of the directing group and one-pot sequential C-H arylation of pyrene carboxamide **2b** followed by directing group removal.

In summary, we have shown the application of the Pd(II)-catalyzed, directing group-aided C-H arylation/alkylation tactics to functionalize the relatively inaccessible C2 and K-region C10 positions of pyrene core. The Pd(II)-catalyzed *β*-C-H arylation/alkylation of the C2-position of pyrene-1-carboxamide possessing 8-aminoquinoline directing group afforded various C1,C2-disubstituted pyrene motifs. Similarly, the Pd(II)-catalyzed selective *γ*-C-H arylation/alkylation of the C10-position of *N*-(pyren-1-yl)picolinamide possessing picolinamide directing group afforded various C1,C10-disubstituted pyrene motifs. Examples of C(9)-H arylation of pyrene-1-carboxamide and the removal of the directing group after the C-H arylation reactions were also shown. The structures of representative pyrene derivatives were confirmed by the X-ray structure analysis. Given the importance of the pyrene derivatives in various fields of chemical sciences, this report is a contribution towards augmentation of the library of pyrene derivatives with C1,C2- and C1,C10-disubstituted pyrene amide motifs. While we have obtained a library of new C1,C2- and C1,C10-disubstituted pyrene amide motifs, currently, we are studying about their structure and photophysical properties and exploring their application, which will be reported in due course.

Experimental Section

General: ^{1}H and $^{13}C\{^{1}H\}$ NMR spectra of compounds were recorded (using TMS as an internal standard) in 400 (or) 500 and ~101 (or) ~126 MHz spectrometers, respectively. The HRMS analysis data of samples were obtained from QTOF mass analyzer by using electrospray ionization (ESI) method. IR spectra of samples were recorded as neat or thin films. Column

chromatography purification was carried out on silica gel (100−200 mesh). Reactions were conducted in anhydrous solvents under a nitrogen atmosphere wherever required. Organic layers obtained after workup were dried by using anhydrous Na_2SO_4. Thin layer chromatography (TLC) analyses were performed on silica gel (silica gel 60 F_{254} plates) or alumina plates and components were visualized by observation under irradiation with UV lamp or iodine vapour. Isolated yields of all the products are reported. Yields of isolated compounds were not optimized. In all of the cases, after the Pd(II)-catalyzed reactions, the respective crude reaction mixtures were subjected to the column chromatographic purification to afford the pure samples. Some pyrene amide products contain some inseparable adventitious grease and hexane residuals or adventitious moisture peaks in the $^{1}H/^{13}C$ NMRs. Adventitious grease and hexane residuals seem to get trapped with the pyrene amide compounds during handling/sample purification. While we have tried to purify all the samples to get pure compounds, however the C-H functionalized pyrene compounds and the starting material pyrene compounds have similar R*f* values and thus, their separation in column chromatography was found to be relatively difficult task. Accordingly, we have repeated column chromatography purification for most of the cases to obtain best possible pure samples in our hand.

Procedures:

Procedure for the synthesis of the carboxamides2a, 2c, 2d: A dry RB flask containing amine (9 mmol, 0.9 equiv), Et_3N (11 mmol, 1.1 equiv) was stirred for 5-10 min under a nitrogen atmosphere. Then, to the reaction flask was added anhydrous DCM (20 mL) followed by dropwise addition of the corresponding acid chloride, which was prepared from pyrene-1-carboxylic acid (10 mmol) and $SOCl_2$ (9 equiv) after refluxing for 12 h. Then, the reaction mixture was stirred overnight and after this period, the reaction mixture was diluted with DCM (10-15 mL) and washed with water (10-15 mL) and twice with saturated aqueous $NaHCO_3$ solution (10-15 mL). The combined organic layers were washed with 1 N HCl (2 x 20 mL) to remove excess amine and then, dried over anhydrous Na_2SO_4, concentrated in vacuum to afford the corresponding carboxamides.

Procedure for the synthesis of the carboxamide 2b: An appropriate amount of picolinic acid (10 mmol), *N*-(3-dimethylaminopropyl)-*N′*-ethylcarbodiimide hydrochloride (1.1 equiv), 1-hydroxybenzotriazole hydrate (1.1 equiv) in DCM (20 mL) were stirred for 1 h at 0 ^{o}C under a nitrogen atmosphere. Then, an appropriate amount of 1-aminopyrene (1 equiv) was added to the above mixture and stirred for 16-24 h at rt. Next, the resulting solution was subjected to aqueous workup and washed with aqueous $NaHCO_3$ solution (two times). Then, the resulting

solution mixture was concentrated and purified on silica gel column chromatography (eluent = EtOAc:hexane) to give the corresponding carboxamide.

Procedure for the Pd(II)-catalyzed arylation of the carboxamides 2a/2d and preparation of the compounds 4/6: A mixture of an appropriate carboxamide (0.2 mmol, 1 equiv), an appropriate aryl iodide (0.8 mmol, 4 equiv), $Pd(OAc)_2$ (4.5 mg, 10 mol%) and AgOAc (0.44 mmol, 2.0-2.2 equiv) in *o*-xylene (2 mL) was heated at 130 ^oC for 24 h in a 10 mL capacity sealed (pressure) tube (the pressure tube was flushed with nitrogen atmosphere for 2 min and it was sealed with a PTFE-lined cap, and then, the tube was heated). After the reaction period, the reaction mixture was concentrated in vacuum and purification of the resulting reaction mixture by column chromatography on neutral alumina or silica gel (eluent = EtOAc:hexane) furnished the corresponding arylated carboxamide (see the corresponding Tables/Schemes for specific examples).

Procedure for the Pd(II)-catalyzed arylation of the carboxamide 2b and preparation of the compounds 5: A mixture of carboxamide **2b** (0.2 mmol, 1 equiv), an appropriate aryl iodide (0.8-1.0 mmol, 4-5 equiv), $Pd(OAc)_2$ (4.5 mg, 10 mol%) and AgOAc (0.44 mmol, 2.2 equiv) in *o*-xylene (2 mL) was heated at 150 ^oC for 36-48 h in a 10 mL capacity sealed (pressure) tube (the pressure tube was flushed with nitrogen atmosphere for 2 min and it was sealed with a PTFE-lined cap, and then, the tube was heated). After the reaction period, the reaction mixture was concentrated in vacuum and purification of the resulting reaction mixture by column chromatography on silica gel (eluent = EtOAc:hexane) furnished the corresponding arylated carboxamide (see the corresponding Tables/Schemes for specific examples).

Procedure for the Pd(II)-catalyzed alkylation of the carboxamide 2a and preparation of the compounds 10: A mixture of carboxamide **2a** (0.14 mmol, 1 equiv), an appropriate alkyl iodide (0.56 mmol, 4 equiv), anhydrous K_2CO_3 (0.28 mmol, 2 equiv), NaOTf (0.42 mmol, 3 equiv), $Pd(OAc)_2$ (10 mol%, 3.4 mg), *t*-AmylOH (2.0 mL) was added in a 10 mL capacity sealed (pressure) tube. The pressure tube was flushed with nitrogen atmosphere for 2 min and it was sealed with a PTFE-lined cap, and then, the tube was heated at 125 ^oC for 48 h. After the reaction period, the reaction mixture was concentrated in vacuum and purification of the resulting reaction mixture by column chromatography on silica gel (eluent = EtOAc:hexane) furnished the corresponding alkylated carboxamide **10** (see the corresponding Tables/Schemes for specific examples).

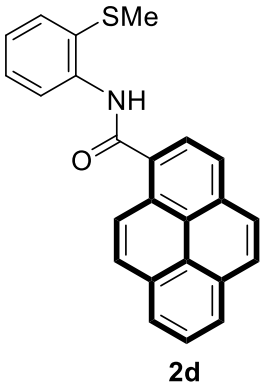
Procedure for the Pd(II)-catalyzed alkylation of the carboxamide 2b and preparation of the compounds 11: A mixture of **2b** carboxamide (0.2 mmol, 1 equiv), an appropriate alkyl

iodide (0.8 mmol, 4.0 equiv), anhydrous KOAc (0.4 mmol, 2 equiv), $Pd(OAc)_2$ (10 mol%, 4.5 mg), 1,4-dioxane (2.0 mL) was added in a 10 mL capacity sealed (pressure) tube. The pressure tube was flushed with nitrogen atmosphere for 2 min and it was sealed with a PTFE-lined cap, and then heated at 130 ^oC for 36 h. After the reaction period, the reaction mixture was concentrated in vacuum and purification of the resulting reaction mixture by column chromatography on neutral alumina or silica gel (eluent = EtOAc:hexane) furnished the corresponding alkylated carboxamide **11** (see the corresponding Tables/Schemes for specific examples).

Procedure for the Pd(II)-catalyzed arylation of the carboxamides 2c and preparation of the compounds 8a,b: A mixture of carboxamide **2c** (0.2 mmol, 1 equiv), an appropriate boronic acid (0.25 mmol, 1.25 equiv), NFSI (0.25 mmol, 1.25 equiv), $Pd(OAc)_2$ (10 mol%, 4.5 mg) was suspended in 1,2-DCE (2.0 mL) in a 10 mL capacity sealed (pressure) tube. The pressure tube was flushed with N_2 for 2 min and sealed with a PTFE-lined cap, and then, the tube was heated at 90 ^oC for 24 h. After the reaction period, the mixture was filtered through a celite® pad and washed with DCM (10-15 mL). The filtrate was concentrated, and the residue was purified by column chromatography on silica gel (eluent = EtOAc:hexane) to afford the corresponding arylated carboxamide **8** (see the corresponding Tables/Schemes for specific examples). The structures of compounds **8a,b** were assigned based on the similar compound prepared under Cu-catalyzed reaction involving aryliodonium salts as arylating reagent in the literature.[15k]

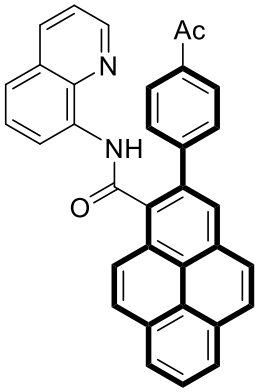
Procedure for the directing group removal/amide hydrolysis and preparation of compound 13: A solution of NaOH (60 mg of NaOH) in EtOH/H_2O (10/1 v/v, 3.3 mL) containing an appropriate arylated carboxamide **5** (0.15 mmol) was refluxed for 24 h. Then, the reaction mixture was cooled to rt and then, the mixture was subjected to evaporation process (to evaporate EtOH) and then, the solution was diluted with water (5 mL). Then, the product was extracted with EtOAc (3 × 5 mL). The organic layers were combined, dried with anhydrous $MgSO_4$ and concentrated. The residue was purified by column chromatography on silica gel (eluent = EtOAc:hexane) to afford the corresponding C-H arylated 1-aminopyrene derivative **13** (see the corresponding Tables/Schemes for specific examples).

***N*-(2-(Methylthio)phenyl)pyrene-1-carboxamide (2d).** Following general procedure, the compound **2d** was obtained after purification by column chromatography on silica gel (EtOAc:hexane = 20:80) as a pale yellow coloured solid (521 mg, 71%, 2 mmol scale); R_f = 0.5 (EtOAc:hexane = 20:80); Mp 149-151 ^oC; IR (DCM): 3275, 2925, 1682, 1513, 1436 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ = 9.08 (s, 1H), 8.79 – 8.72 (m, 2H), 8.31 (d, 1H, J = 7.9 Hz), 8.26 – 8.19 (m, 4H), 8.15 (d, 1H, J = 8.9 Hz), 8.09 – 8.05 (m, 2H), 7.58 (d, 1H, J = 7.7 Hz), 7.47 (t, 1H, J = 7.5 Hz), 7.22 – 7.18 (m, 1H), 2.40 (s, 3H); ^{13}C NMR (~101 MHz, $CDCl_3$): δ = 168.0, 138.7, 133.0, 133.0, 131.2, 130.7, 130.7, 129.1, 129.0, 129.0, 127.1, 126.5, 126.1, 126.0, 125.9, 124.9, 124.9, 124.7, 124.6, 124.4, 120.9, 19.1; HRMS (ESI): *m/z* $[M + Na]^+$ calculated for $C_{24}H_{17}NNaOS$: 390.0929 found 390.0922.



2d

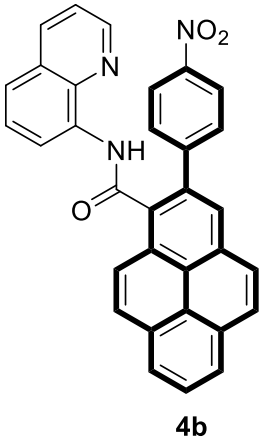
2-(4-Acetylphenyl)-*N*-(quinolin-8-yl)pyrene-1-carboxamide (4a). Following general procedure, the compound **4a** was obtained after purification by column chromatography on silica gel (EtOAc:hexane = 20:80) as a pale yellow coloured solid (68 mg, 70%);R_f = 0.4 (EtOAc:hexane = 20:80);Mp 249-251 ^oC; IR (DCM): 3338, 1679, 1519, 1483, 1264 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ = 10.04 (s, 1H), 8.99 (d, 1H, J = 7.5 Hz), 8.55 – 8.54 (m, 1H), 8.49 (d, 1H, J = 9.2 Hz), 8.27 – 8.25 (m, 3H), 8.19 (d, 2H, J = 9.0 Hz), 8.14 – 8.06 (m, 3H), 7.95 (d, 2H, J = 8.2 Hz), 7.90 (d, 2H, J = 8.3 Hz), 7.62 (t, 1H, J = 8.1 Hz), 7.55 (d, 1H, J = 8.2 Hz), 7.36 (dd, 1H, J_1 = 8.2 Hz, J_2 = 4.2 Hz), 2.52 (s, 3H); ^{13}C NMR (~101 MHz, $CDCl_3$): δ = 196.8, 166.8, 147.1, 144.7, 137.4, 135.2, 135.0, 134.8, 133.3, 130.9, 130.3, 130.1, 129.7, 128.6, 128.3, 128.1, 127.8, 127.4, 126.8, 126.3, 126.0, 125.5, 125.0, 124.9, 124.9, 123.5, 123.1, 123.0, 121.1, 120.5, 115.7, 25.6; HRMS (ESI): *m/z* $[M + H]^+$ calculated for $C_{34}H_{23}N_2O_2$: 491.1760 found 491.1779.



4a

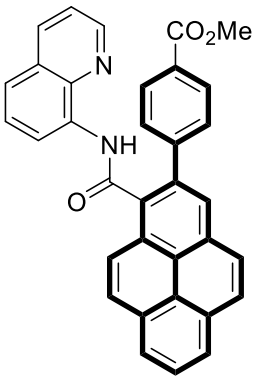
2-(4-Nitrophenyl)-*N*-(quinolin-8-yl)pyrene-1-carboxamide (4b). Following general procedure, the compound **4b** was obtained after purification by column chromatography on silica gel (EtOAc:hexane = 25:75) as a pale yellow coloured solid (84 mg, 86%); R_f = 0.3

(EtOAc:hexane = 20:80; Mp 237-239 ^{o}C; IR (DCM): 2924, 1670, 1595, 1519, 1341 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6): δ = 10.61 (s, 1H), 8.73 (d, 1H, J = 4.0 Hz), 8.61 (d, 1H, J = 7.5 Hz), 8.47 (s, 1H), 8.43 – 8.32 (m, 7H), 8.27 (d, 2H, J = 8.6 Hz), 8.17 (t, 1H, J = 7.6 Hz), 8.05 (d, 2H, J = 8.6 Hz), 7.76 (d, 1H, J = 8.2 Hz), 7.66 (t, 1H, J = 7.8 Hz), 7.56 (dd, 1H, J_1 = 8.3 Hz, J_2 = 4.2 Hz); ^{13}C NMR (~101 MHz, $CDCl_3$): δ = 167.5, 148.2, 147.6, 147.2, 138.3, 136.3, 134.8, 134.2, 132.0, 131.2, 130.8, 130.3, 129.6, 129.4, 128.9, 127.9, 127.3, 127.0, 126.8, 126.3, 126.1, 125.7, 124.5, 124.3, 124.1, 123.6, 123.6, 122.4, 121.7, 116.8; HRMS (ESI): *m/z* [M + H]$^{+}$ calculated for $C_{32}H_{20}N_3O_3$: 494.1505 found 494.1520.



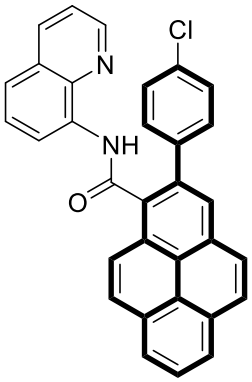
4b

Methyl 4-(1-(quinolin-8-ylcarbamoyl)pyren-2-yl)benzoate (4c). Following general procedure, the compound **4c** was obtained after purification by column chromatography on silica gel (EtOAc:hexane = 20:80) as a pale yellow coloured solid (58 mg, 58%); R_f = 0.4 (EtOAc:hexane = 20:80); Mp 160-162 ^{o}C; IR (DCM): 3348, 2940, 1725, 1675, 1528 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 10.03 (s, 1H), 8.99 (d, 1H, J = 7.5 Hz), 8.54 (d, 1H, J = 3.1 Hz), 8.48 (d, 1H, J = 9.2 Hz), 8.26 – 8.23 (m, 3H), 8.17 (d, 1H, J = 9.0 Hz), 8.12 – 8.03 (m, 5H), 7.89 (d, 1H, J = 7.8 Hz), 7.63 – 7.59 (m, 1H), 7.53 (d, 1H, J = 8.2 Hz), 7.34 (dd, 1H, J_1 = 8.1 Hz, J_2 = 4.1 Hz), 3.86 (s, 3H); ^{13}C NMR (~101 MHz, $CDCl_3$): δ = 167.9, 166.9, 148.1, 145.6, 138.4, 136.2, 136.0, 134.4, 131.9, 131.3, 131.1, 130.7, 129.7, 129.5, 129.3, 129.1, 129.1, 128.8, 127.8, 127.3, 127.0, 126.5, 126.0, 125.9, 124.5, 124.2, 124.0, 122.2, 121.6, 116.9, 52.1; HRMS (ESI): *m/z* [M + H]$^{+}$ calculated for $C_{34}H_{23}N_2O_3$: 507.1709 found 507.1695.



4c

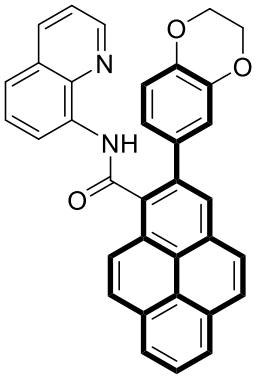
2-(4-Chlorophenyl)-*N*-(quinolin-8-yl)pyrene-1-carboxamide (4d). Following general procedure, the compound **4d** was obtained after purification by column chromatography on silica gel (EtOAc:hexane = 20:80) as a pale coloured yellow solid (51 mg, 53%); R_f = 0.5 (EtOAc:hexane = 20:80); Mp 237-239 ^{o}C;



4d

IR (DCM): 3348, 2936, 1663, 1528, 1490 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ = 10.02 (s, 1H), 9.01 – 9.00 (m, 1H), 8.56 (dd, 1H, J_1 = 4.1 Hz, J_2 = 1.4 Hz), 8.47 (d, 1H, J = 9.2 Hz), 8.27 – 8.24 (m, 3H), 8.19 – 8.05 (m, 5H), 7.74 (d, 2H, J = 8.4 Hz), 7.64 (t, 1H, J = 7.8 Hz), 7.58 – 7.56 (m, 1H), 7.38 (dd, 1H, J_1 = 8.3 Hz, J_2 = 4.2 Hz), 7.34 (d, 2H. J = 8.4 Hz); ^{13}C NMR (~101 MHz, $CDCl_3$): δ = 168.0, 148.1, 139.3, 138.4, 136.2, 135.9, 134.4, 133.7, 132.0, 131.4, 131.1, 130.7, 129.2, 129.0, 128.8, 128.6, 127.9, 127.3, 127.1, 126.5, 126.1, 126.0, 125.9, 124.6, 124.2, 123.9, 122.2, 121.6, 116.8; HRMS (ESI): *m/z* $[M + H]^+$ calculated for $C_{32}H_{20}ClN_2O$: 483.1264 found 483.1252.

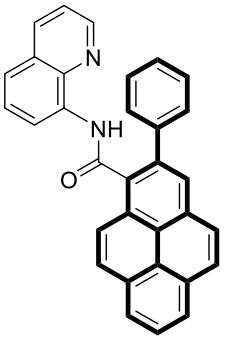
2-(2,3-Dihydrobenzo[*b*][1,4]dioxin-6-yl)-*N*-(quinolin-8-yl)pyrene-1-carboxamide (4e).



4e

Following general procedure, the compound **4e** was obtained after purification by column chromatography on silica gel (EtOAc:hexane = 20:80) as a pale yellow coloured solid (45 mg, 45%); R_f = 0.4 (EtOAc:hexane = 20:80); Mp 248 – 250 ^oC; IR (DCM): 3338, 2924, 1667, 1516, 1323 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ = 10.02 (s, 1H), 9.04 (d, 1H, J = 7.6 Hz), 8.59 (d, 1H, J = 4.0 Hz), 8.48 (d, 1H, J = 9.2 Hz), 8.26 – 8.23 (m, 3H), 8.19 – 8.11 (m, 4H), 8.05 (t, 1H, J = 7.6 Hz), 7.64 (t, 1H, J = 7.9 Hz), 7.55 (d, 1H, J = 8.2 Hz), 7.39 – 7.34 (m, 2H), 7.29 – 7.26 (m, 1H), 6.81 (d, 1H, J = 8.3 Hz), 4.17 – 4.16 (m, 4H); ^{13}C NMR (~101 MHz, $CDCl_3$): δ = 168.3, 148.0, 143.4, 143.2, 138.5, 136.7, 136.1, 134.7, 134.2, 131.9, 131.4, 131.1, 130.7, 129.0, 128.8, 128.8, 127.8, 127.4, 127.2, 126.3, 125.8, 125.7, 124.7, 124.3, 123.6, 122.6, 121.8, 121.5, 118.5, 117.2, 116.7, 64.3, 64.2; HRMS (ESI): *m/z* $[M + H]^+$ calculated for $C_{34}H_{23}N_2O_3$: 507.1709 found 507.1724.

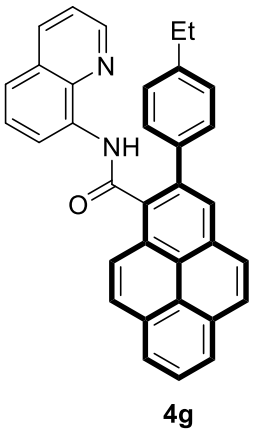
2-Phenyl-*N*-(quinolin-8-yl)pyrene-1-carboxamide (4f). Following general procedure, the compound **4f** was obtained after purification by column chromatography on silica gel (EtOAc:hexane = 20:80) as a pale yellow coloured solid (49 mg, 55%); R_f = 0.5 (EtOAc:hexane = 20:80); Mp 218-220 ^oC; IR (DCM): 3342, 1667, 1519, 1483, 1325 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ = 9.96 (s, 1H), 8.97 (dd, 1H, J_1 = 7.6 Hz, J_2 = 1.0 Hz), 8.52 (dd, 1H, J_1 = 4.1 Hz, J_2 = 1.4 Hz), 8.47 (d, 1H, J = 9.3 Hz), 8.27 (s, 1H), 8.23 (t, 2H, J = 7.9 Hz), 8.17 – 8.03 (m, 5H), 7.83 – 7.77 (m, 2H), 7.60 – 7.56 (m, 1H), 7.50 (d, 1H, J = 8.3 Hz), 7.34 – 7.31 (m, 3H), 7.18 (t, 1H, J = 7.5 Hz); ^{13}C NMR (~126



4f

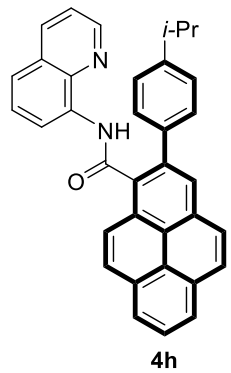
MHz, $CDCl_3$): δ = 168.2, 148.0, 140.8, 138.4, 137.3, 136.1, 134.6, 131.9, 131.6, 131.2, 130.8, 129.4, 129.0, 128.9, 128.8, 128.4, 127.8, 127.5, 127.3, 127.2, 126.4, 126.3, 125.9, 125.8, 124.7, 124.4, 123.8, 121.8, 121.5, 116.6; HRMS (ESI): *m/z* $[M + H]^+$ calculated for $C_{32}H_{21}N_2O$: 449.1654 found 449. 1649.

2-(4-Ethylphenyl)-*N*-(quinolin-8-yl)pyrene-1-carboxamide (4g). Following general procedure, the compound **4g** was obtained after purification by column chromatography on silica gel (EtOAc:hexane = 20:80) as a pale yellow coloured solid (67 mg, 71%); R_f = 0.6 (EtOAc:hexane = 20:80); Mp 205-207 ^oC; IR (DCM): 3338, 1665, 1515, 1482, 1324 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ = 9.99 (s, 1H), 9.02 (d, 1H, J = 7.6 Hz), 8.55 – 8.49 (m, 2H), 8.30 (s, 1H), 8.26 – 8.23 (m, 2H), 8.19 – 8.05 (m, 5H), 7.71 (d, 2H, J = 8.0 Hz), 7.62 (t, 1H, J = 8.0 Hz), 7.53 (d, 1H, J = 8.0 Hz), 7.33 (dd, 1H, J_1 = 8.4 Hz, J_2 = 4.0 Hz), 7.17 (d, 2H, J = 8.0 Hz), 2.53 (q, 2H, J = 7.6 Hz), 1.05 (t, 3H, J = 7.6 Hz); ^{13}C NMR (~101 MHz, $CDCl_3$): δ = 168.4, 147.9, 143.5, 138.4, 138.1, 137.3, 135.9, 134.7, 131.9, 131.5, 131.1, 130.7, 129.4, 129.0, 128.8, 128.8, 128.0, 127.8, 127.3, 127.1, 126.4, 126.2, 125.8, 125.7, 124.7, 124.3, 123.6, 121.8, 121.4, 116.6, 28.5, 15.4; HRMS (ESI): *m/z* $[M + H]^+$ calculated for $C_{34}H_{25}N_2O$: 477.1967 found 477.1982.



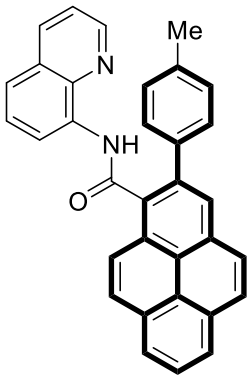
4g

2-(4-Isopropylphenyl)-*N*-(quinolin-8-yl)pyrene-1-carboxamide (4h). Following general procedure, the compound **4h** was obtained after purification by column chromatography on silica gel (EtOAc:hexane = 20:80) as a pale yellow coloured solid (65 mg, 66%); R_f = 0.5 (EtOAc:hexane = 20:80); Mp 160-162 ^oC; IR (DCM): 3337, 2959, 1662, 1519, 1481 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ = 9.99 (s, 1H), 9.03 (dd, 1H, J_1 = 7.6 Hz, J_2 = 0.9 Hz), 8.55 – 8.51 (m, 2H), 8.28 (s, 1H), 8.24 – 8.22 (m, 2H), 8.18 – 8.03 (m, 5H), 7.74 (d, 1H, J = 8.1 Hz), 7.60 (t, 1H, J = 8.0 Hz), 7.49 (dd, 1H, J_1 = 8.3 Hz, J_2 = 0.9 Hz), 7.32 - 7.28 (m, 1H), 7.19 (d, 2H, J = 8.1 Hz), 2.80 – 2.72 (m, 1H), 1.05 (d, 6H, J = 6.9 Hz); ^{13}C NMR (~101 MHz, $CDCl_3$): δ = 168.3, 148.0, 147.8, 138.3, 138.2, 137.3, 135.8, 134.7, 131.9, 131.4, 131.0, 130.6, 129.4, 128.9, 128.8, 128.7, 127.6, 127.2, 127.1, 126.4, 126.3, 126.2, 125.7, 125.6, 124.7, 124.3, 123.6, 121.7, 121.3, 116.4, 33.6, 23.7; HRMS (ESI): *m/z* $[M + H]^+$ calculated for $C_{35}H_{27}N_2O$: 491.2123 found 491.2142.



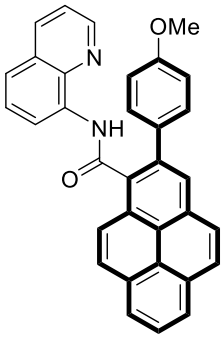
4h

***N*-(Quinolin-8-yl)-2-(*p*-tolyl)pyrene-1-carboxamide (4i).** Following general procedure, the compound **4i** was obtained after purification by column chromatography on silica gel (EtOAc:hexane = 20:80) as a pale yellow coloured solid (54 mg, 58%); R_f = 0.5 (EtOAc:hexane = 20:80); Mp 195-197 ^oC; IR (DCM): 3355, 3052, 1690, 1536, 1321 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ = 10.04 (s, 1H), 9.04 (d, 1H, J = 7.5 Hz), 8.54 (dd, 1H, J_1 = 4.0 Hz, J_2 = 1.4 Hz), 8.48 (d, 1H, J = 9.2 Hz), 8.27 – 8.21 (m, 3H), 8.16 – 8.03 (m, 5H), 7.72 (d, 2H, J = 7.9 Hz), 7.62 (t, 1H, J = 8.1 Hz), 7.51 (d, 1H, J = 8.2 Hz), 7.32 (dd, 1H, J_1 = 8.2 Hz, J_2 = 4.2 Hz), 7.18 (d, 2H, J = 7.8 Hz), 2.26 (s, 3H); ^{13}C NMR (~101 MHz, $CDCl_3$): δ = 168.4, 148.0, 138.4, 137.9, 137.2, 136.0, 134.7, 131.9, 131.5, 131.1, 130.7, 129.3, 129.2, 128.0, 128.8, 128.7, 127.8, 127.3, 127.2, 126.4, 126.3, 125.8, 125.7, 124.7, 124.3, 123.6, 121.9, 121.5, 116.7, 21.1; HRMS (ESI): *m/z* $[M + H]^+$ calculated for $C_{33}H_{23}N_2O$: 463.1810 found 463.1791.



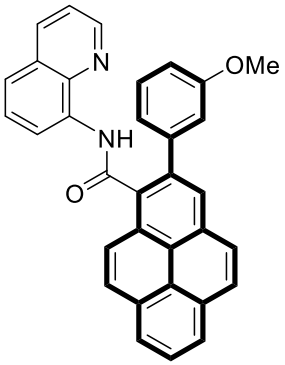
4i

2-(4-Methoxyphenyl)-*N*-(quinolin-8-yl)pyrene-1-carboxamide (4j). Following general procedure, the compound **4j** was obtained after purification by column chromatography on silica gel (EtOAc:hexane = 25:75) as a pale yellow coloured solid (64 mg, 67%); R_f = 0.4 (EtOAc:hexane = 20:80); Mp 178-180 ^oC; IR (DCM): 3336, 2932, 1682, 1521, 1321 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ = 10.02 (s, 1H), 9.05 (d, 1H, J = 7.5 Hz), 8.55 – 8.54 (m, 1H), 8.48 (d, 1H, J = 9.2 Hz), 8.26 – 8.22 (m, 3H), 8.16 (d, 2H, J = 9.1 Hz), 8.12 – 8.03 (m, 3H), 7.75 (d, 2H, J = 7.7 Hz), 7.62 (t, 1H, J = 7.9 Hz), 7.53 (d, 1H, J = 8.2 Hz), 7.33 (dd, 1H, J_1 = 7.8 Hz, J_2 = 4.0 Hz), 6.91 (d, 2H, J = 7.8 Hz), 3.71 (s, 3H); ^{13}C NMR (~101 MHz, $CDCl_3$): δ = 168.5, 159.1, 148.0, 138.4, 136.9, 136.1, 134.7, 133.2, 131.9, 131.5, 131.1, 130.7, 130.6, 129.0, 128.8, 128.8, 127.8. 127.3, 127.2, 126.4, 126.3, 125.8, 125.7, 124.7, 124.3, 123.5, 121.9, 121.5, 116.6, 113.9, 55.2; HRMS (ESI): *m/z* $[M + H]^+$ calculated for $C_{33}H_{23}N_2O_2$: 479.1760 found 479.1775.



4j

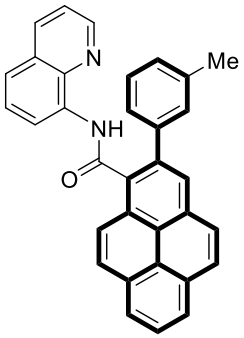
2-(3-Methoxyphenyl)-*N*-(quinolin-8-yl)pyrene-1-carboxamide (4k). Following general procedure, the compound **4k** was obtained after purification by column chromatography on silica gel (EtOAc:hexane = 20:80) as a pale yellow coloured solid (73 mg, 77%); R_f = 0.4 (EtOAc:hexane = 20:80);



4k

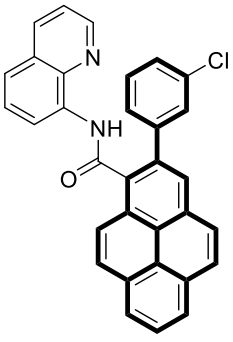
Mp 201-203 °C; IR (DCM): 3337, 1665, 1516, 1482, 1324 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ = 10.04 (s, 1H), 9.03 (d, 1H, J = 7.6 Hz), 8.55 (d, 1H, J = 3.9 Hz), 8.50 (d, 1H, J = 9.2 Hz), 8.29 (s, 1H), 8.23 (d, 2H, J = 7.6 Hz), 8.18 – 8.14 (m, 2H), 8.11 – 8.03 (m, 3H), 7.61 (t, 1H, J = 7.9 Hz), 7.52 (d, 1H, J = 8.3 Hz), 7.41 – 7.39 (m, 2H), 7.33 (dd, 1H, J_1 = 8.0 Hz, J_2 = 4.0 Hz), 7.26 – 7.24 (m, 1H), 6.77 (d, 1H, J = 7.9 Hz), 3.75 (s, 3H); ^{13}C NMR (~101 MHz, $CDCl_3$): δ = 168.3, 159.5, 148.0, 142.2, 138.4, 137.1, 136.1, 134.7, 131.9, 131.5, 131.1, 130.7, 129.4, 129.1, 128.9, 128.8, 127.8, 127.3, 127.1, 126.3, 126.2, 125.9, 125.8, 124.7, 124.3, 123.8, 122.0, 121.9, 121.5, 116.7, 114.5, 113.9, 55.3; HRMS (ESI): *m/z* $[M + H]^+$ calculated for $C_{33}H_{23}N_2O_2$: 479.1760 found 479.1780.

***N*-(Quinolin-8-yl)-2-(*m*-tolyl)pyrene-1-carboxamide (4l).** Following general procedure, the compound **4l** was obtained after purification by column chromatography on silica gel (EtOAc:hexane = 20:80) as a pale yellow coloured solid (57 mg, 84%, 0.15 mmol scale); R_f = 0.5 (EtOAc:hexane = 20:80); Mp 186-188 °C; IR (DCM): 3333, 1667, 1519, 1483, 1325 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ = 10.01 (s, 1H), 9.01 (d, 1H, J = 7.6 Hz), 8.56 (d, 1H, J = 4.0 Hz), 8.51 (d, 1H, J = 9.2 Hz), 8.28 (s, 1H), 8.26 – 8.23 (m, 2H), 8.17 (d, 2H, J = 9.2 Hz), 8.13 – 8.04 (m, 3H), 7.63 – 7.59 (m, 3H), 7.52 (d, 1H, J = 8.2 Hz), 7.34 (dd, 1H, J_1 = 8.2 Hz, J_2 = 4.2 Hz), 7.22 (t, 1H, J = 7.6 Hz), 7.01 (d, 1H, J = 7.6 Hz), 2.30 (s, 3H); ^{13}C NMR (~101 MHz, $CDCl_3$): δ = 168.3, 148.0, 140.7, 138.4, 137.9, 137.5, 136.1, 134.7, 131.9, 131.6, 131.1, 130.7, 130.2, 129.0, 128.8, 128.7, 128.2, 128.2, 127.8, 127.3, 127.2, 126.5, 126.3, 125.8, 125.7, 124.7, 124.4, 123.7, 121.8, 121.5, 116.6, 21.4; HRMS (ESI): *m/z* $[M + H]^+$ calculated for $C_{33}H_{23}N_2O$: 463.1810 found 463.1827.



4l

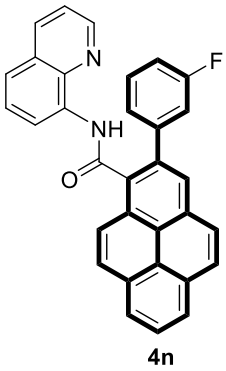
2-(3-Chlorophenyl)-*N*-(quinolin-8-yl)pyrene-1-carboxamide (4m). Following general procedure, the compound **4m** was obtained after purification by column chromatography on silica gel (EtOAc:hexane = 20:80) as a pale yellow coloured solid (71 mg, 74%); R_f = 0.5 (EtOAc:hexane = 20:80); Mp 218-220 °C; IR (DCM): 3334, 2923, 1668, 1519, 1483 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ = 9.96 (s, 1H), 8.95 (dd, 1H, J_1 = 7.6 Hz, J_2 = 1.0 Hz), 8.57 (dd, 1H, J_1 = 4.1 Hz, J_2 = 1.6 Hz), 8.48 (d, 1H, J = 9.2 Hz), 8.26 – 8.23 (m, 3H), 8.19 – 8.16 (m, 2H), 8.12 – 8.04 (m, 3H), 7.80 (t, 1H, J =



4m

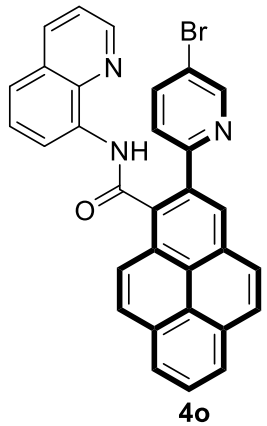
1.8 Hz), 7.63 – 7.58 (m, 2H), 7.52 (dd, 1H, J_1 = 8.4 Hz, J_2 = 1.1 Hz), 7.35 (dd, 1H, J_1 = 8.3 Hz, J_2 = 4.2 Hz), 7.18 (t, 1H, J = 7.7 Hz), 7.14 – 7.12 (m, 1H); ^{13}C NMR (~126 MHz, $CDCl_3$): δ = 167.8, 148.2, 142.6, 138.4, 136.1, 135.8, 134.5, 134.3, 132.0, 131.4, 131.2, 130.8, 129.6, 129.5, 129.3, 129.1, 128.9, 127.8, 127.6, 127.5, 127.3, 127.1, 126.5, 126.0, 126.0, 125.9, 124.7, 124.3, 124.0, 122.0, 121.6, 116.7; HRMS (ESI): *m/z* $[M + H]^+$ calculated for $C_{32}H_{20}ClN_2O$: 483.1264 found 483.1261.

2-(3-Fluorophenyl)-*N*-(quinolin-8-yl)pyrene-1-carboxamide (4n). Following general procedure, the compound **4n** was obtained after purification by column chromatography on silica gel (EtOAc:hexane = 20:80) as a pale yellow coloured solid (61 mg, 66%); R_f = 0.5 (EtOAc:hexane = 20:80); Mp 217 – 219 ^{o}C; IR (DCM): 3342, 1667, 1519, 1483, 1423 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 10.03 (s, 1H), 9.00 (d, 1H, J = 7.6 Hz), 8.54 (d, 1H, J = 3.9 Hz), 8.47 (d, 1H, J = 9.2 Hz), 8.21 – 8.10 (m, 5H), 8.06 – 8.01 (m, 3H), 7.62 – 7.54 (m, 3H), 7.50 (d, 1H, J = 8.3 Hz), 7.33 – 7.25 (m, 2H), 6.91 (t, 1H, J = 8.1 Hz); ^{13}C NMR (~101 MHz, $CDCl_3$): δ = 167.9, 162.7 (d, $J_{C\text{-}F}$ = 245 Hz), 148.1, 143.0 (d, $J_{C\text{-}F}$ = 5.3 Hz), 138.3, 136.1, 135.8 (d, $J_{C\text{-}F}$ = 1.5 Hz), 134.5, 131.9, 131.3, 131.1, 130.7, 129.9 (d, $J_{C\text{-}F}$ = 8.4 Hz), 129.2, 129.0, 128.8, 127.8, 127.3, 127.0, 126.5, 126.0, 125.8, 125.3 (d, $J_{C\text{-}F}$ = 2.5 Hz), 124.6, 124.1, 123.9, 122.1, 121.6, 116.7, 116.5 (d, $J_{C\text{-}F}$ = 22.0 Hz), 114.4 (d, $J_{C\text{-}F}$ = 21.0 Hz); HRMS (ESI): *m/z* $[M + H]^+$ calculated for $C_{32}H_{20}FN_2O$: 467.1560 found 467.1574.



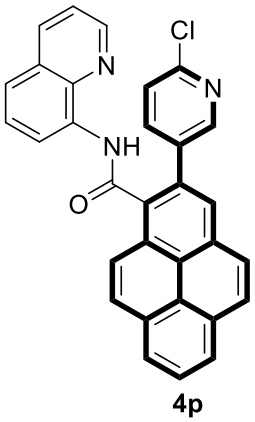
4n

2-(5-Bromopyridin-2-yl)-*N*-(quinolin-8-yl)pyrene-1-carboxamide (4o). Following general procedure, the compound **4o** was obtained after purification by column chromatography on silica gel (EtOAc:hexane = 20:80) as a pale yellow coloured solid (61 mg, 58%); R_f = 0.4 (EtOAc:hexane = 20:80); Mp 115 – 117 ^{o}C; IR (DCM): 3338, 2924, 1667, 1519, 1483 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 10.13 (s, 1H), 9.05 (d, 1H, J = 7.3 Hz), 8.70 (d, 1H, J = 1.8 Hz), 8.57 – 8.51 (m, 3H), 8.27 – 8.06 (m, 7H), 7.84 (d, 1H, J = 8.4 Hz), 7.77 (dd, 1H, J_1 = 8.4 Hz, J_2 = 2.2 Hz), 7.67 (t, 1H, J = 8.0 Hz), 7.59 (d, 1H, J = 7.7 Hz), 7.38 (dd, 1H, J_1 = 8.3 Hz, J_2 = 4.2 Hz); ^{13}C NMR (~101 MHz, $CDCl_3$): δ = 168.3, 156.6, 150.6, 148.2, 139.0, 138.5, 136.1, 134.7, 134.4, 132.0, 131.3, 131.1, 130.8, 129.2, 129.0, 127.9, 127.3, 127.3, 126.7, 126.0, 125.9, 125.7, 125.2, 124.6, 124.6, 124.1, 122.1, 121.6, 119.8, 116.9; HRMS (ESI): *m/z* $[M + H]^+$ calculated for $C_{31}H_{19}BrN_3O$: 528.0711 found 528.0685.



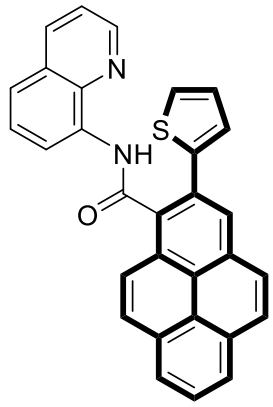
4o

2-(6-Chloropyridin-3-yl)-*N*-(quinolin-8-yl)pyrene-1-carboxamide (4p). Following general procedure, the compound **4p** was obtained after purification by column chromatography on silica gel (EtOAc:hexane = 20:80) as a pale yellow coloured solid (23 mg, 48%, 0.1 mmol scale); R_f = 0.4 (EtOAc:hexane = 20:80); Mp 135 – 137 °C; IR (DCM): 3344, 2917, 1682, 1536, 1332 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ = 10.64 (s, 1H), 8.78 (d, 1H, J = 2.3 Hz), 8.74 (dd, 1H, J_1 = 4.2 Hz, J_2 = 1.5 Hz), 8.62 – 8.60 (m, 1H), 8.47 (s, 1H), 8.43 – 8.30 (m, 7H), 8.23 (dd, 1H, J_1 = 8.2 Hz, J_2 = 2.5 Hz), 8.16 (t, 1H, J = 7.6 Hz), 7.79 – 7.77 (m, 1H), 7.69 – 7.65 (m, 1H), 7.60 – 7.57 (m, 2H); ^{13}C NMR (~101 MHz, $CDCl_3$): δ = 167.4, 150.7, 149.7, 148.3, 139.5, 138.3, 136.3, 135.5, 134.1, 132.1, 132.0, 131.4, 131.2, 130.7, 129.6, 129.4, 129.0, 127.9, 127.3, 126.9, 126.8, 126.3, 126.1, 125.8, 124.4, 124.2, 124.1, 123.8, 122.5, 121.7, 117.1; HRMS (ESI): *m/z* $[M + H]^+$ calculated for $C_{31}H_{19}ClN_3O$: 484.1217 found 484.1205.



4p

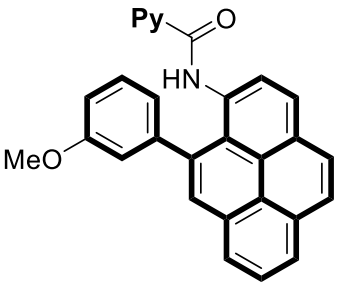
***N*-(Quinolin-8-yl)-2-(thiophen-2-yl)pyrene-1-carboxamide (4q).** Following general procedure, the compound **4q** was obtained after purification by column chromatography on silica gel (EtOAc:hexane = 20:80) as a pale yellow coloured solid (48 mg, 54%); R_f = 0.4 (EtOAc:hexane = 20:80); Mp 221 – 223 °C; IR (DCM): 3332, 2921, 1667, 1525, 1467 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ = 10.54 (s, 1H), 8.83 (d, 1H, J = 7.4 Hz), 8.72 (d, 1H, J = 4.0 Hz), 8.56 (s, 1H), 8.43 – 8.25 (m, 7H), 8.16 – 8.15 (m, 1H), 7.79 (d, 1H, J = 8.2 Hz), 7.74 – 7.72 (m, 1H), 7.63 – 7.56 (m, 3H), 7.12 – 7.10 (m, 1H); ^{13}C NMR (~101 MHz, DMSO-d_6): δ = 167.8, 149.6, 141.8, 138.8, 137.1, 134.7, 131.8, 131.4, 131.2, 130.6, 129.8, 129.5, 129.3, 128.5, 128.4, 128.4, 128.2, 127.8, 127.6, 127.5, 127.4, 126.8, 126.5, 126.3, 124.6, 123.8, 1235, 123.2, 122.7, 118.1; HRMS (ESI): *m/z* $[M + H]^+$ calculated for $C_{30}H_{19}N_2OS$: 455.1218 found 455.1199.



4q

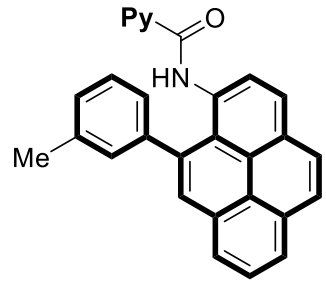
***N*-(10-(3-Methoxyphenyl)pyren-1-yl)picolinamide (5a).** Following general procedure, the compound **5a** was obtained after purification by column chromatography on silica gel (EtOAc:hexane = 25:75) as a brown coloured solid (61 mg, 71%); R_f = 0.3 (EtOAc:hexane = 20:80); Mp 167 - 169 °C; IR (DCM): 3475, 3352, 1667, 1602, 1517 cm^{-1};

^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.86 (s, 1H), 8.69 (d, 1H, J = 8.3 Hz), 8.32 – 8.28 (m, 2H), 8.18 (d, 2H, J = 7.6 Hz), 8.12 – 8.06 (m, 3H), 8.04 – 7.98 (m, 1H), 7.94 (s, 1H), 7.82 (t, 1H, J = 7.6 Hz), 7.40 – 7.37 (m, 1H), 7.15 – 7.11 (m, 3H), 6.55 – 6.54 (m, 1H), 3.74 (s, 3H); ^{13}C NMR (~101 MHz, $CDCl_3$): δ = 162.2, 159.6, 149.8, 147.4, 144.3, 137.1, 136.5, 131.3, 131.3, 130.3, 129.4, 129.4, 127.7, 126.6, 126.4, 126.3, 126.1, 126.0, 125.4, 124.8, 124.3, 124.0, 122.0, 121.8, 121.4, 113.7, 113.2, 55.1; HRMS (ESI): *m/z* $[M + H]^+$ calculated for $C_{29}H_{21}N_2O_2$: 429.1603 found 429.1593.



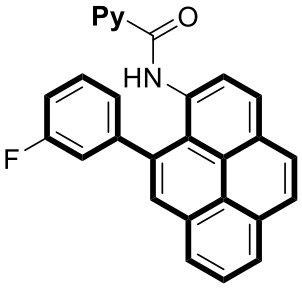
5a

***N*-(10-(*m*-Tolyl)pyren-1-yl)picolinamide (5b).** Following general procedure, the compound **5b** was obtained after purification by column chromatography on silica gel (EtOAc:hexane = 20:80) as a brown coloured solid (46 mg, 57%); R_f = 0.5 (EtOAc:hexane = 20:80); Mp 167-169 ^{o}C; IR (DCM): 3325, 3040, 1690, 1517, 1478 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.80 (s, 1H), 8.71 (d, 1H, J = 8.4 Hz), 8.31 – 8.26 (m, 2H), 8.20 – 8.18 (m, 2H), 8.12 – 8.05 (m, 3H), 8.01 (t, 1H, J = 7.6 Hz), 7.93 (s, 1H), 7.81 (td, 1H, J_1 = 7.7 Hz, J_2 = 1.1 Hz), 7.39 – 7.36 (m, 3H), 7.14 (t, 1H, J = 7.6 Hz), 6.81 (d, 1H, J = 7.6 Hz), 2.24 (s, 3H); ^{13}C NMR (~101 MHz, $CDCl_3$): δ = 162.1, 149.8, 147.3, 142.9, 137.9, 137.0, 136.8, 131.4, 131.3, 130.4, 129.7, 129.4, 128.3, 127.8, 127.6, 126.6, 126.5, 126.3, 126.1, 126.0, 125.9, 125.3, 124.7, 124.3, 124.0, 122.1, 121.9, 21.3; HRMS (ESI): *m/z* $[M + H]^+$ calculated for $C_{29}H_{21}N_2O$: 413.1654 found 413.1639.



5b

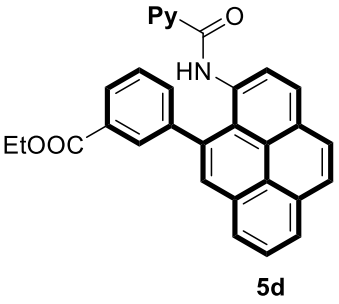
***N*-(10-(3-Fluorophenyl)pyren-1-yl)picolinamide (5c).** Following general procedure, the compound **5b** was obtained after purification by column chromatography on silica gel (EtOAc:hexane = 20:80) as a brown coloured solid (47 mg, 57%); R_f = 0.5 (EtOAc:hexane = 20:80); Mp 195-197 ^{o}C; IR (DCM): 3328, 2921, 1671, 1521, 1486 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.80 (s, 1H), 8.70 (d, 1H, J = 8.4 Hz), 8.35 – 8.34 (m, 1H), 8.30 (d, 1H, J = 8.4 Hz), 8.22 – 8.18 (m, 2H), 8.13 – 8.00 (m, 4H), 7.92 (s, 1H), 7.84 (td, 1H, J_1 = 7.7 Hz, J_2 = 1.7 Hz), 7.43 – 7.36 (m, 2H), 7.25 – 7.23 (m, 1H), 7.16 – 7.10 (m, 1H), 6.73 – 6.68 (m, 1H); ^{13}C NMR (~101 MHz, $CDCl_3$): δ = 162.9 (d, $J_{C\text{-}F}$ = 245.2 Hz), 162.0, 149.6, 147.4, 145.2 (d, $J_{C\text{-}F}$ = 7.8 Hz), 137.2, 135.2 (d, $J_{C\text{-}F}$ = 1.7 Hz), 131.6, 131.3, 131.2, 130.1, 129.7 (d, $J_{C\text{-}F}$ = 8.5 Hz), 129.4, 127.8, 126.6, 126.4, 126.3,



5c

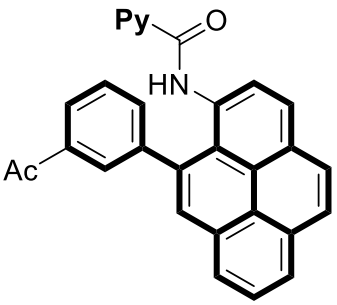
126.2, 125.7, 125.1, 125.0 (d, $J_{C\text{-}F}$ = 2.8 Hz), 124.9, 124.4, 123.9, 122.0, 121.8, 115.9 (d, $J_{C\text{-}F}$ = 21.8 Hz), 113.5 ($J_{C\text{-}F}$ = 20.8 Hz); HRMS (ESI): *m/z* $[M + H]^+$ calculated for $C_{28}H_{18}FN_2O$: 417.1403 found 417.1393.

Ethyl 3-(3-(picolinamido)pyren-4-yl)benzoate (5d). Following general procedure, the compound **5d** was obtained after purification by column chromatography on silica gel (EtOAc:hexane = 20:80) as a brown coloured solid (59 mg, 63%); R_f = 0.4 (EtOAc:hexane = 20:80); Mp 157-159 °C; IR (DCM): 3328, 2921, 1671, 1521, 1486cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.72 (s, 1H), 8.68 (d, 1H. *J* = 8.4 Hz), 8.36 – 8.31 (m, 2H), 8.23 (d, 1H, *J* = 7.3 Hz), 8.18 – 8.09 (m, 5H), 8.04 (t, 1H, *J* = 7.6 Hz), 7.96 (s, 1H), 7.81 (td, J_1 = 7.7 Hz, J_2 = 1.6 Hz), 7.71 (d, 1H, *J* = 7.8 Hz), 7.66 – 7.64 (m, 1H), 7.39 – 7.36 (m, 1H), 7.24 (t, 1H, *J* = 7.7 Hz), 4.45 – 4.39 (m, 2H), 1.43 (t, 3H, *J* = 7.1 Hz); ^{13}C NMR (~101 MHz, $CDCl_3$): δ = 166.5, 161.8, 149.5, 147.4, 143.2, 137.1, 135.6, 133.6, 131.9, 131.3, 131.0, 130.7, 130.2, 129.5, 129.5, 128.1, 128.1, 127.7, 126.7, 126.4, 126.3, 126.2, 125.7, 124.9, 124.4, 124.1, 121.9, 121.9, 61.01, 14.5; HRMS (ESI): *m/z* $[M + H]^+$ calculated for $C_{31}H_{23}N_2O_3$: 471.1709 found 471.1716.



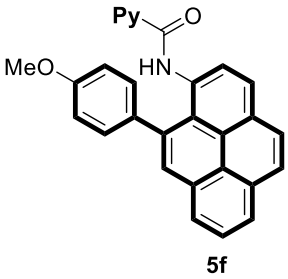
5d

***N*-(10-(3-Acetylphenyl)pyren-1-yl)picolinamide (5e).** Following general procedure, the compound **5e** was obtained after purification by column chromatography on silica gel (EtOAc:hexane = 20:80) as a brown coloured solid (52 mg, 59%); R_f = 0.3 (EtOAc:hexane = 20:80); Mp 168-170 °C; IR (DCM): 3440, 1686, 1602, 1513, 1248 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6): δ = 10.03 (s, 1H), 8.42 (d, 1H, *J* = 8.3 Hz), 8.36 – 8.21 (m, 6H), 8.11 (t, 1H, *J* = 7.6 Hz), 8.01 (s, 1H), 7.99 (s, 1H), 7.93 – 7.86 (m, 2H), 7.67 (d, 1H, *J* = 7.5 Hz), 7.56 – 7.53 (m, 1H), 7.41 (d, 1H, *J* = 7.9 Hz), 7.28 (t, 1H, *J* = 7.7 Hz), 2.46 (s, 3H); ^{13}C NMR (~101 MHz, $CDCl_3$): δ = 197.9, 161.8, 149.3, 147.4, 143.4, 137.3, 136.9, 135.5, 133.4, 131.9, 131.2, 130.8, 130.1, 129.6, 129.0, 128.5, 127.7, 126.8, 126.5, 126.4, 126.3, 126.3, 126.2, 125.7, 125.0, 124.6, 124.3, 122.2, 121.8, 26.7; HRMS (ESI): *m/z* $[M + H]^+$ calculated for $C_{30}H_{21}N_2O_2$: 441.1603 found 441.1589.



5e

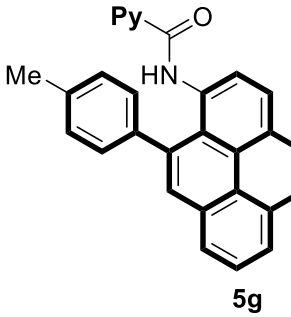
***N*-(10-(4-Methoxyphenyl)pyren-1-yl)picolinamide (5f).** Following general procedure, the compound **5f** was obtained after purification by column chromatography on silica gel (EtOAc:hexane = 20:80) as a brown coloured solid (42 mg, 50%);



5f

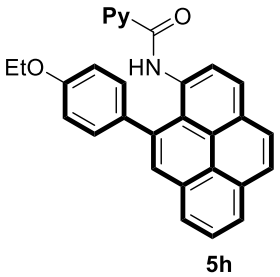
R_f = 0.4 (EtOAc:hexane = 20:80); Mp 171 – 173 °C; IR (DCM): 3396, 2951, 1678, 1556, 1514 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ = 9.98 (s, 1H), 8.80 (d, 1H, J = 8.4 Hz), 8.32 – 8.29 (m, 2H), 8.22 – 8.19 (m, 2H), 8.15 – 8.01 (m, 4H), 7.95 (s, 1H), 7.87 – 7.83 (m, 1H), 7.51 (d, 2H, J = 8.8 Hz), 7.41 – 7.38 (m, 1H), 6.81 (d, 2H, J = 8.4 Hz), 3.63 (s, 3H); ^{13}C NMR (~101 MHz, $CDCl_3$): δ = 162.0, 159.0, 150.0, 147.5, 137.0, 136.2, 135.2, 131.6, 131.5, 131.3, 130.4, 130.1, 129.2, 127.7, 126.5, 126.5, 126.3, 126.1, 125.8, 125.2, 124.6, 124.3, 123.4, 121.9, 121.7, 113.8, 55.0; HRMS (ESI): *m/z* $[M + H]^+$ calculated for $C_{29}H_{21}N_2O_2$: 429.1603 found 429.1588.

***N*-(10-(*p*-Tolyl)pyren-1-yl)picolinamide (5g).** Following general procedure, the compound **5g** was obtained after purification by column chromatography on silica gel (EtOAc:hexane = 20:80) as a brown coloured solid (51 mg, 62%); R_f = 0.5 (EtOAc:hexane = 20:80); Mp 158 – 160 °C; IR (DCM): 3348, 3048, 1682, 1521, 1325 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ = 9.88 (s, 1H), 8.75 (d, 1H, J = 8.4 Hz), 8.31 – 8.26 (m, 2H), 8.19 (d, 2H, J = 7.7 Hz), 8.13 – 8.05 (m, 3H), 8.01 (t, 1H, J = 7.6 Hz), 7.93 (s, 1H), 7.8 (td, 1H, J_1 = 7.7 Hz, J_2 = 1.6 Hz), 7.46 (d, 2H, J = 8.0 Hz), 7.38 – 7.35 (m, 1H), 7.06 (d, 2H, J = 7.8 Hz), 2.13 (s, 3H); ^{13}C NMR (~101 MHz, $CDCl_3$): δ = 162.0, 150.0, 147.4, 140.0, 137.0, 136.7, 136.6, 131.5, 131.3, 130.4, 129.3, 129.0, 128.9, 127.8, 126.5, 126.3, 126.1, 125.8, 125.3, 124.7, 124.3, 123.6, 121.9, 21.1; HRMS (ESI): *m/z* $[M + H]^+$ calculated for $C_{29}H_{21}N_2O$: 413.1654 found 413.1669.



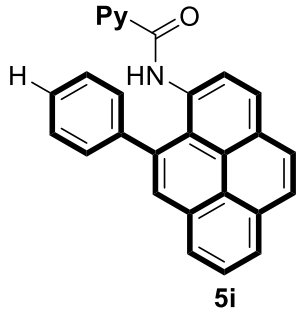
5g

***N*-(10-(4-Ethoxyphenyl)pyren-1-yl)picolinamide (5h).** Following general procedure, the compound **5h** was obtained after purification by column chromatography on silica gel (EtOAc:hexane = 20:80) as a brown coloured solid (53 mg, 61%);R_f = 0.4 (EtOAc:hexane = 20:80); Mp 148 – 150 °C; IR (DCM): 3296, 2926, 1674, 1511, 1495 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ = 9.97 (s, 1H), 8.79 (d, 1H, J = 8.4 Hz), 8.30 – 8.29 (m, 2H), 8.19 – 8.17 (m, 2H), 8.12 – 7.99 (m, 4H), 7.93 (s, 1H), 7.84–8.0 (m, 1H), 7.47 (d, 2H, J = 8.6 Hz), 7.38 – 7.35 (m, 1H), 6.77 (d, 2H, J = 8.6 Hz), 3.78 (q, 2H, J = 7.0 Hz), 1.35 (t, 3H, J = 7.0 Hz); ^{13}C NMR (~101 MHz, $CDCl_3$): δ = 162.0, 158.4, 150.0, 147.5, 137.0, 136.3, 135.0, 131.6, 131.5, 131.3, 130.4, 130.1, 129.2, 127.8, 126.5, 126.5, 126.3, 126.1, 125.7, 125.2, 124.6, 124.3, 123.3, 121.9, 121.7, 114.2, 63.1, 14.9; HRMS (ESI): *m/z* $[M + H]^+$ calculated for $C_{30}H_{23}N_2O_2$: 443.1760 found 443.1775.



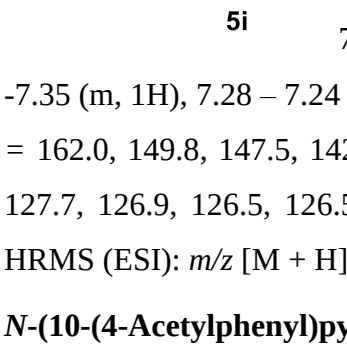
5h

***N*-(10-Phenylpyren-1-yl)picolinamide (5i).** Following general procedure, the compound **5i** was obtained after purification by column chromatography on silica gel (EtOAc:hexane = 20:80) as a brown coloured solid (48 mg, 60%); R_f = 0.5 (EtOAc:hexane = 20:80); Mp 167 – 169 ^oC; IR (DCM): 3347, 2923, 1678, 1511, 839 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ = 9.85 (s, 1H), 8.75 (d, 1H, J = 8.4 Hz), 8.31 (d, 1H, J = 8.4 Hz), 8.25 (d, 1H, J = 4.6 Hz), 8.22 – 8.00 (m, 6H), 7.94 (s, 1H), 7.81 (td, 1H, J_1 = 7.6 Hz, J_2 = 1.4 Hz), 7.57 (d, 2H, J = 7.3 Hz), 7.38 -7.35 (m, 1H), 7.28 – 7.24 (m, 2H), 7.04 (t, 1H, J = 7.5 Hz); ^{13}C NMR (~101 MHz, $CDCl_3$): δ = 162.0, 149.8, 147.5, 142.9, 137.0, 136.6, 131.7, 131.5, 131.3, 130.3, 129.3, 129.0, 128.3, 127.7, 126.9, 126.5, 126.5, 126.3, 126.1, 125.9, 125.4, 124.8, 124.3, 123.6, 121.9, 121.7; HRMS (ESI): *m/z* $[M + H]^+$ calculated for $C_{28}H_{19}N_2O$: 399.1497 found 399.1511.



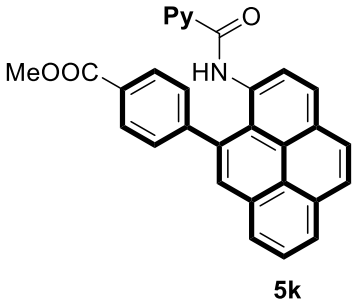
5i

***N*-(10-(4-Acetylphenyl)pyren-1-yl)picolinamide (5j).** Following general procedure, **5j** was obtained after purification by column chromatography on silica gel (EtOAc:hexane = 25:75) as a brown coloured solid (54 mg, 61%); R_f = 0.3 (EtOAc:hexane = 20:80); Mp 158 – 160 ^oC. IR (DCM): 3452, 3344, 1682, 1605, 1517 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ = 9.54 (s, 1H), 8.56 (d, 1H, J = 8.3 Hz), 8.25 (d, 1H, J = 8.3 Hz), 8.18 – 8.13 (m, 3H), 8.09 – 8.04 (m, 3H), 8.00 – 7.98 (m, 1H), 7.87 (s, 1H), 7.79 – 7.76 (m, 3H), 7.57 (d, 2H, J = 7.8 Hz), 7.30 – 7.28 (m, 1H), 2.36 (s, 1H); ^{13}C NMR (~101 MHz, $CDCl_3$): δ = 197.3, 161.9, 149.5, 148.0, 147.4, 137.1, 135.5, 135.3, 131.5, 131.2, 130.8, 130.0, 129.6, 129.1. 128.3, 127.7, 126.7, 126.5, 126.3, 126.3, 126.1, 125.8, 125.1, 124.5, 124.3, 122.0, 121.9, 26.4; HRMS (ESI): *m/z* $[M + H]^+$ calculated for $C_{30}H_{21}N_2O_2$: 441.1603 found 441.1624.



5j

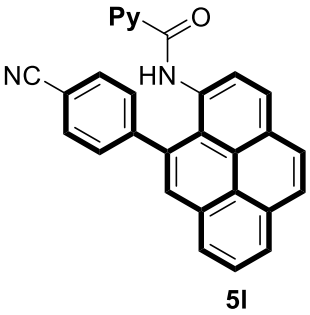
Methyl 4-(3-(picolinamido)pyren-4-yl)benzoate (5k). Following general procedure, the compound **5k** was obtained after purification by column chromatography on silica gel (EtOAc:hexane = 25: 75) as a brown coloured solid (58 mg, 64%); R_f = 0.3 (EtOAc:hexane = 20:80); Mp 125^oC – 127 ^oC; IR (DCM): 3500, 1716, 1678, 1512, 1434 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ = 9.59 (s, 1H), 8.61 (d, 1H, J = 8.3 Hz), 8.29 (d, 1H, J = 8.4 Hz), 8.22 – 8.20 (m, 2H), 8.15 – 8.05 (m, 4H), 8.02 (t, 1H, J = 7.6 Hz), 7.92 (s, 1H), 7.88 (d, 2H, J = 8.3 Hz), 7.79 (td, 1H, J_1 = 7.6 Hz, J_2 = 1.6 Hz), 7.60 (d, 2H, J = 8.2 Hz), 7.32 – 7.28 (m, 1H),



5k

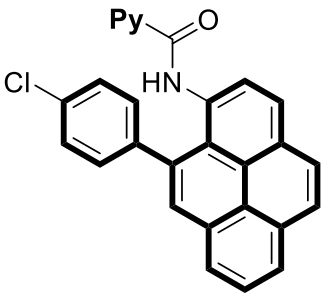
3.87 (s, 3H); ^{13}C NMR (~101 MHz, $CDCl_3$): δ = 166.6, 162.0, 149.5, 147.8, 147.5, 137.1, 135.7, 131.5, 131.3, 131.0, 130.1, 129.6, 129.5, 128.9, 128.5, 127.7, 126.7, 126.4, 126.4, 126.3, 125.9, 125.8, 125.1, 124.4, 124.4, 122.0, 121.9, 51.9; HRMS (ESI): *m/z* $[M + H]^+$ calculated for $C_{30}H_{21}N_2O_3$: 457.1552 found 457.1535.

***N*-(10-(4-Cyanophenyl)pyren-1-yl)picolinamide (5l).** Following general procedure, the compound **5l** was obtained after purification by column chromatography on silica gel (EtOAc:hexane = 20:80) as a brown coloured solid (47 mg, 56%); R_f = 0.4 (EtOAc:hexane = 20:80); Mp 213 – 215 ^{o}C; IR (DCM): 3322, 2924, 2226, 1679, 1513 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.54 (s, 1H), 8.56 (d, 1H, *J* = 8.3 Hz), 8.35 – 8.32 (m, 2H), 8.26 (d, 1H, *J* = 7.5 Hz), 8.19 – 8.10 (m, 4H), 8.06 (t, 1H, *J* = 7.6 Hz), 7.93 – 7.89 (m, 2H), 7.65 (d, 2H, *J* = 8.3 Hz), *7*.53 – 7.48 (m, 3H); ^{13}C NMR (~101 MHz, $CDCl_3$): δ = 161.9, 149.3, 148.0, 147.5, 137.6, 134.8, 131.9, 131.8, 131.2, 130.6, 129.9, 129.8, 129.6, 127.8, 126.9, 126.8, 126.6, 126.5, 126.4, 126.2, 125.3, 124.8, 124.5, 122.0. 118.6, 110.3; HRMS (ESI): *m/z* $[M + H]^+$ calculated for $C_{29}H_{18}N_3O$: 424.1450 found 424.1467.



5l

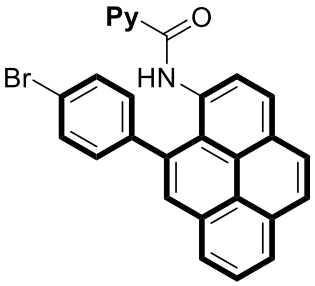
***N*-(10-(4-Chlorophenyl)pyren-1-yl)picolinamide (5m).** Following general procedure, **5m** was obtained after purification by column chromatography on silica gel (EtOAc:hexane = 20:80) as a brown coloured solid (37 mg, 58%, 0.15 mmol scale); R_f = 0.5 (EtOAc:hexane = 20:80); Mp 200 – 202 ^{o}C; IR (DCM): 3440, 3332, 1678, 1517, 1486 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6): δ = 10.04 (s, 1H), 8.44 – 8.40 (m, 3H), 8.33 (d, 1H, *J* = 7.5 Hz), 8.28 (d, 1H, *J* = 7.5 Hz), 8.25 – 8.19 (m, 2H), 8.09 (t, 1H, *J* = 7.6 Hz), 7.99 – 7.97 (m, 3H), 7.62 – 7.58 (m, 1H), 7.44 (d, 2H, *J* = 8.2 Hz), 7.21 (d, 2H, *J* = 8.2 Hz); ^{13}C NMR (~101 MHz, $CDCl_3$): δ = 162.0, 149.5, 147.7, 141.5, 137.2, 135.4, 133.2, 131.7, 131.3, 131.2, 130.3, 130.2, 129.4, 128.5, 127.8, 126.6, 126.4, 126.4, 126.3, 126.3, 125.6, 124.9, 124.4, 123.9, 121.9, 121.7; HRMS (ESI): *m/z* $[M + H]^+$ calculated for $C_{28}H_{18}ClN_2O$: 433.1108 found 433.1100.



5m

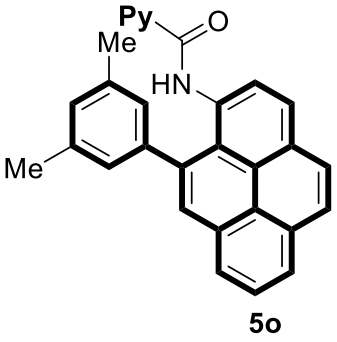
***N*-(10-(4-Bromophenyl)pyren-1-yl)picolinamide (5n).** Following general procedure, the compound **5n** was obtained after purification by column chromatography on silica gel (EtOAc:hexane = 20:80) as a brown coloured solid (50 mg, 53%);

R_f = 0.5 (EtOAc:hexane = 20:80); Mp 165 – 167 °C; IR (DCM): 3325, 2959, 1678, 1521, 1467 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ = 10.08 (s, 1H), 8.46 – 8.29 (m, 6H), 8.26 – 8.21 (m, 2H), 8.11 (t, 1H, J = 7.6 Hz), 8.00 – 7.96 (m, 3H), 7.63 – 7.60 (m, 1H), 7.39 (d, 2H, J = 8.4 Hz), 7.35 (d, 2H, J = 8.4 Hz); ^{13}C NMR (~126 MHz, $CDCl_3$): δ = 161.0, 148.4, 146.8, 140.9, 136.2, 134.3, 130.6, 130.4, 130.3, 130.1, 129.6, 129.1, 128.4, 126.7, 125.6, 125.4, 125.3, 124.6, 123.9, 123.4, 123.0, 120.9, 120.7, 120.3; HRMS (ESI): *m/z* $[M + H]^+$ calculated for $C_{28}H_{18}BrN_2O$: 477.0603 found 477.0607.



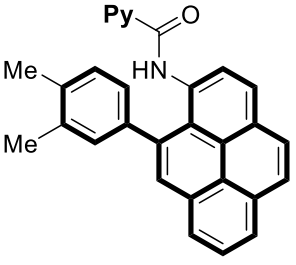
5n

***N*-(10-(3,5-Dimethylphenyl)pyren-1-yl)picolinamide (5o).** Following general procedure, the compound **5o** was obtained after purification by column chromatography on silica gel (EtOAc:hexane = 20:80) as a brown coloured solid (38 mg, 45%); R_f = 0.5 (EtOAc:hexane = 20:80); Mp 165 – 167 °C; IR (DCM): 3313, 1678, 1511, 1434, 840 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ = 9.75 (s, 1H), 8.65 (d, 1H, J = 8.4 Hz), 8.31 – 8.28 (m, 2H), 8.19 (d, 2H, J = 7.4 Hz), 8.13 – 8.06 (m, 3H), 8.01 (t, 1H, J = 7.6 Hz), 7.93 (s, 1H), 7.83 (td, 1H, J_1 = 7.7 Hz, J_2 = 1.6 Hz), 7.41-7.38 (m, 1H), 7.16 (s, 2H), 6.59 (s, 1H), 2.20 (s, 6H); ^{13}C NMR (~101 MHz, $CDCl_3$): δ = 162.1, 149.8, 147.2, 142.9, 137.8, 136.9, 131.4, 131.3, 131.1, 130.4, 129.5, 128.4, 127.8, 126.8, 126.6, 126.5, 126.3, 126.0, 125.9, 125.3, 124.7, 124.3, 122.4, 121.8, 21.2; HRMS (ESI): *m/z* $[M + H]^+$ calculated for $C_{30}H_{23}N_2O$: 427.1810 found 427.1826.



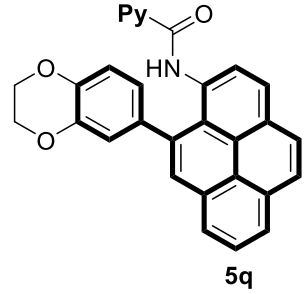
5o

***N*-(10-(3,4-Dimethylphenyl)pyren-1-yl)picolinamide (5p).** Following general procedure, the compound **5p** was obtained after purification by column chromatography on silica gel (EtOAc:hexane = 20:80) as a brown coloured solid (55 mg, 65%); R_f = 0.5 (EtOAc:hexane = 20:80); Mp 148 – 150 °C; IR (DCM): 3428, 1686, 1590, 1517, 1128 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ = 9.88 (s, 1H), 8.44 – 8.38 (m, 2H), 8.33 – 8.18 (m, 5H), 8.08 (t, 1H, J = 7.6 Hz), 7.98 – 7.95 (m, 3H), 7.59 – 7.55 (m, 1H), 7.19 (s, 1H), 7.15 – 7.12 (m, 1H), 6.92 (d, 1H, J = 7.6 Hz), 2.04 (s, 3H), 1.90 (s, 3H); ^{13}C NMR (~101 MHz, $CDCl_3$): δ = 162.0, 150.0, 147.3, 140.5, 136.9, 136.8, 136.4, 135.3, 131.4, 131.3, 130.5, 130.3, 129.7, 129.4, 127.8, 126.6, 126.5, 126.3, 126.3, 126.3, 126.0, 125.8, 125.2, 124.7, 124.3, 124.1, 122.2, 121.8, 19.5, 19.3; HRMS (ESI): *m/z* $[M + H]^+$ calculated for $C_{30}H_{23}N_2O$: 427.1810 found 427.1801.



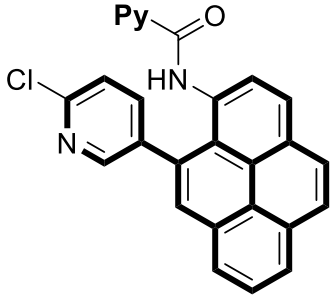
5p

***N*-(10-(2,3-Dihydrobenzo[*b*][1,4]dioxin-6-yl)pyren-1-yl)picolinamide (5q).** Following general procedure, the compound **5q** was obtained after purification by column chromatography on silica gel (EtOAc:hexane = 20:80) as a brown coloured solid (56 mg, 62%). R_f = 0.3 (EtOAc:hexane = 20:80); Mp 192 – 194 °C; IR (DCM): 3448, 2925, 1686, 1517, 1252 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ = 10.06 (s, 1H), 8.79 (d, 1H, J = 8.3 Hz), 8.43 – 8.42 (m, 1H), 8.30 – 8.23 (m, 2H), 8.18 (d, 1H, J = 7.1 Hz), 8.11 – 7.98 (m, 4H), 7.92 (s, 1H), 7.86 (t, 1H, J_1 = 7.7 Hz, J_2 = 1.6 Hz), 7.44 – 7.41 (m, 1H), 7.10 – 7.06 (m, 2H), 6.84 (d, 1H, J = 8.0 Hz), 4.20 – 4.13 (m, 2H), 3.98 – 3.91 (m, 2H); ^{13}C NMR (~101 MHz, $CDCl_3$): δ = 161.9, 150.1, 147.5, 143.4, 143.0, 137.2, 136.2, 136.0, 131.5, 131.5, 131.3, 130.4, 129.2, 127.7, 126.5, 126.3, 126.1, 125.9, 125.3, 124.7, 124.3, 123.4, 122.3, 122.1, 121.7, 118.0, 117.3, 64.3, 64.2; HRMS (ESI): *m/z* $[M + H]^+$ calculated for $C_{30}H_{21}N_2O_3$: 457.1552 found 457.1541.



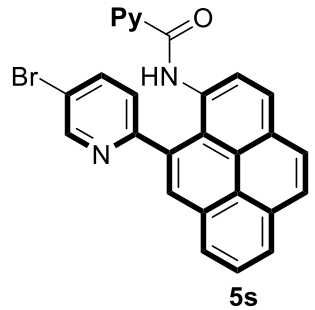
5q

***N*-(10-(6-Chloropyridin-3-yl)pyren-1-yl)picolinamide (5r).** Following general procedure, the compound **5r** was obtained after purification by column chromatography on silica gel (EtOAc:hexane = 25:75) as a brown coloured solid (36 mg, 42%); R_f = 0.3 (EtOAc:hexane = 20:80); Mp 194 – 196 °C; IR (DCM): 3323, 1678, 1513, 1274, 842 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ = 9.72 (s, 1H), 8.72 (s, 1H), 8.65 (d, 1H, J = 8.3 Hz), 8.43 (d, 1H, J = 4.4 Hz), 8.23 – 8.17 (m, 3H), 8.09 – 7.97 (m, 4H), 7.88 (t, 1H, J = 7.6 Hz), 7.81 (s, 1H), 7.56 (d, 1H, J = 8.1 Hz), 7.47 (t, 1H, J = 6.2 Hz), 6.99 (d, 1H, J = 8.2 Hz); ^{13}C NMR (~101 MHz, $CDCl_3$): δ = 161.6, 150.1, 149.1, 148.4, 148.0, 139.4, 137.6, 137.5, 132.3, 131.3, 131.2, 130.7, 129.8, 129.4, 127.7, 126.7, 126.6, 126.5, 126.3, 126.1, 125.2, 124.4, 123.7, 123.4, 122.0, 121.3; HRMS (ESI): *m/z* $[M + H]^+$ calculated for $C_{27}H_{17}ClN_3O$: 434.1060 found 434.1045.



5r

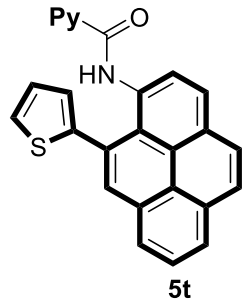
***N*-(10-(5-Bromopyridin-2-yl)pyren-1-yl)picolinamide (5s).** Following general procedure, the compound **5s** was obtained after purification by column chromatography on silica gel (EtOAc:hexane = 25:75) as a brown coloured solid (48 mg, 51%); R_f = 0.3 (EtOAc:hexane = 20:80); Mp 175 – 177 °C; IR (DCM): 3344, 2936, 1682, 1521, 1236 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ = 9.80 (s, 1H), 8.80 – 8.79 (m, 1H), 8.50 – 8.47 (m, 2H), 8.33 (d, 1H, J = 8.3 Hz), 8.26 (d, 1H, J = 7.6 Hz), 8.19 – 8.12 (m, 4H), 8.10 – 8.03 (m, 2H), 7.87 (td, 1H, J_1 = 7.7 Hz, J_2 = 1.6 Hz), 7.60 (dd, 1H,



5s

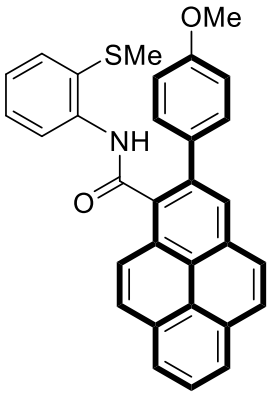
J_1 = 8.4 Hz, J_2 = 2.4 Hz), 7.49 – 7.45 (m, 1H), 7.42 (d, 1H, J = 8.3 Hz); ^{13}C NMR (~101 MHz, $CDCl_3$): δ = 162.5, 160.2, 150.6, 149.3, 147.9, 138.7, 137.4, 134.7, 132.4, 131.2, 130.6, 130.0, 129.9, 127.8, 126.9, 126.5, 126.4, 126.4, 126.2, 125.6, 125.5, 125.4, 124.7, 122.8, 122.1, 118.9; HRMS (ESI): *m/z* $[M + H]^+$ calculated for $C_{27}H_{17}BrN_3O$: 478.0555 found 478.0538.

***N*-(10-(Thiophen-2-yl)pyren-1-yl)picolinamide (5t).** Following general procedure, the compound **5t** was obtained after purification by column chromatography on silica gel (EtOAc:hexane = 20:80) as a brown coloured solid (57 mg, 71%); R_f = 0.5 (EtOAc:hexane = 20:80); Mp 148 – 150 ^{o}C; IR (DCM): 3428, 2932, 1675, 1513, 1321 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 10.31 (s, 1H), 8.84 (d, 1H, J = 8.4 Hz), 8.41 (d, 1H, J = 4.3 Hz), 8.32 (d, 1H, J = 8.4 Hz), 8.23 (d, 2H, J = 7.6 Hz), 8.15 – 8.01 (m, 5H), 7.88 – 7.84 (m, 1H), 7.44 – 7.41 (m, 1H), 7.25 (dd, 1H, J_1 = 7.6 Hz, J_2 = 0.9 Hz), 7.17 (dd, 1H, J_1 = 5.2 Hz, J_2 = 0.9 Hz), 6.91 (dd, 1H, J_1 = 5.2 Hz, J_2 = 3.6 Hz); ^{13}C NMR (~101 MHz, $CDCl_3$): δ = 162.2, 150.0, 147.6, 143.8, 137.1, 133.5, 131.7, 131.3, 129.9, 129.1, 128.6, 127.8, 127.6, 127.2, 126.4, 126.3, 126.3, 126.0, 125.8, 125.7, 124.9, 124.6, 123.4, 122.0, 121.9; HRMS (ESI): *m/z* $[M + H]^+$ calculated for $C_{26}H_{17}N_2OS$: 405.1062 found 405.1073.



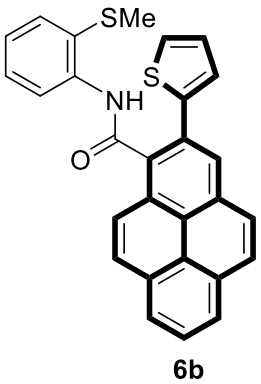
5t

2-(4-Methoxyphenyl)-*N*-(2-(methylthio)phenyl)pyrene-1-carboxamide (6a). Following general procedure, the compound **6a** was obtained after purification by column chromatography on silica gel (EtOAc:hexane = 20:80) as a brown coloured solid (53 mg, 56%). R_f = 0.4 (EtOAc:hexane = 20:80); Mp 151 – 153 ^{o}C. IR (DCM): 3348, 2925, 1667, 1582, 1509 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.58 (d, 1H, J = 8.1 Hz), 8.49 (s, 1H), 8.44 (d, 1H, J = 9.2 Hz), 8.25 – 8.04 (m, 7H), 7.76 (d, 2H, J = 8.6 Hz), 7.46 – 7.38 (m, 2H), 7.14 – 7.10 (m, 1H), 7.02 (d, 2H, J = 8.6 Hz), 3.83 (s, 3H), 2.05 (s, 3H); ^{13}C NMR (~101 MHz, $CDCl_3$): δ = 168.5, 159.4, 138.4, 136.3, 133.1, 133.0, 132.0, 131.1, 130.6, 129.1, 128.9, 128.7, 127.1, 126.3, 126.3, 126.1, 125.9, 125.8, 124.8, 124.5, 124.3, 123.5, 120.8, 114.3, 55.4, 18.9; HRMS (ESI): *m/z* $[M + H]^+$ calculated for $C_{31}H_{24}NO_2S$: 474.1528 found 474.1538.



6a

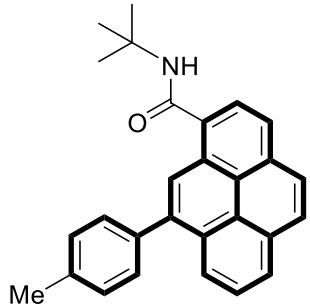
***N*-(2-(Methylthio)phenyl)-2-(thiophen-2-yl)pyrene-1-carboxamide (6b).** Following general procedure, the compound **6b** was obtained after purification by column chromatography on silica gel (EtOAc:hexane = 20:80) as a brown coloured solid (51 mg, 57%); R_f = 0.5 (EtOAc:hexane = 20:80); Mp 167 – 169 ^{o}C; IR (DCM): 3336, 2921, 1678, 1509, 1428 cm^{-1};



6b

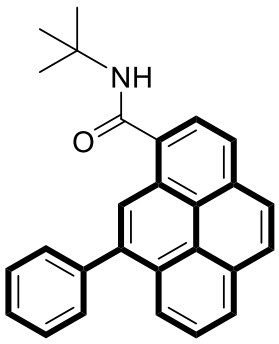
^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.69 – 8.64 (m, 2H), 8.39 – 8.36 (m, 2H), 8.28 – 8.25 (m, 2H), 8.21 – 8.19 (m, 2H), 8.14 – 8.06 (m, 2H), 7.55 (d, 1H, *J* = 3.1 Hz), 7.50 – 7.41 (m, 3H), 7.17 – 7.12 (m, 2H), 2.08 (s, 3H); ^{13}C NMR (~101 MHz, DMSO-d_6): δ = 168.2, 141.9, 135.6, 135.1, 132.3, 131.4, 131.2, 130.7, 129.7, 129.2, 129.1, 128.4, 128.0, 128.0, 127.6, 127.6, 127.3, 127.0, 127.0, 126.5, 126.3, 126.3, 125.6, 125.3, 123.9, 123.3; HRMS (ESI): *m/z* $[M + H]^+$ calculated for $C_{28}H_{20}NOS_2$: 450.0986 found 450.0999.

***N*-(*Tert*-butyl)-9-(*p*-tolyl)pyrene-1-carboxamide (8a).** Following general procedure, the compound **8a** was obtained after purification by column chromatography on silica gel (EtOAc:hexane = 20:80) as a pale yellow coloured solid (41 mg, 53%); R_f = 0.5 (EtOAc:hexane = 20:80); Mp 161 -163 ^{o}C; IR (DCM): 3259, 2959, 1675, 1632, 1540 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.50 (s, 1H), 8.30 (d, 1H, *J* = 7.9 Hz), 8.25 (d, 1H, *J* = 7.6 Hz), 8.16 – 8.13 (m, 2H), 8.10 – 8.06 (m, 2H), 7.99 (t, 1H, *J* = 7.8 Hz), 7.59 (d, 2H, *J* = 7.9 Hz), 7.40 (d, 2H, *J* = 7.8 Hz), 6.00 – 5.99 (m, 1H), 2.54 (s, 3H), 1.59 (s, 9H); ^{13}C NMR (~101 MHz, $CDCl_3$): δ = 169. 6, 140.6, 137.9, 137.3, 132.6, 132.1, 131.4, 130.2, 130.1, 129.2, 128.6, 128.1, 127.0, 126.1, 125.9, 124.9, 124.7, 124.7, 124.6, 124.3, 124.1, 52.3, 29.1, 21.4; HRMS (ESI): *m/z* $[M + H]^+$ calculated for $C_{28}H_{26}NO$: 392.2014 found 392.1998.



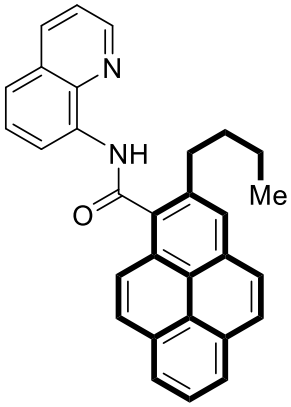
8a

***N*-(*Tert*-butyl)-9-phenylpyrene-1-carboxamide (8b).** Following general procedure, the compound **8b** was obtained after purification by column chromatography on silica gel (EtOAc:hexane = 20:80) as a pale yellow coloured solid (41 mg, 55%); R_f = 0.5 (EtOAc:hexane = 20:80); Mp 158 -160 ^{o}C; IR (DCM): 3340, 2925, 1707, 1673, 1518 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.51 (s, 1H), 8.27 – 8.22 (m, 2H), 8.14 – 7.97 (m, 5H), 7.69 (d, 2H, *J* = 7.1 Hz), 7.60 (t, 2H, *J* = 7.6 Hz), 7.54 (d, 1H, *J* = 7.2 Hz), 6.08 (s, 1H), 1.59 (s, 9H); ^{13}C NMR (~101 MHz, $CDCl_3$): δ = 169.5, 140.8, 140.6, 132.6, 132.1, 131.4, 130.2, 130.0, 128.6, 128.5, 128.0, 127.6, 127.0, 126.1, 125.9, 124.9, 124.8, 124.6, 124.6, 124.2. 124.1, 52.3, 29.1; HRMS (ESI): *m/z* $[M + H]^+$ calculated for $C_{27}H_{24}NO$: 378.1858 found 378.1845.



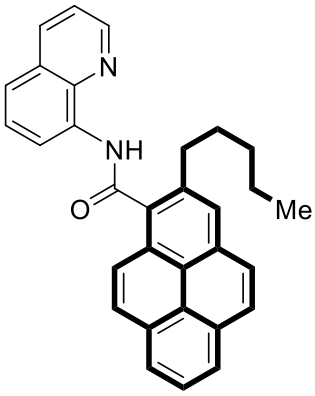
8b

2-Butyl-*N*-(quinolin-8-yl)pyrene-1-carboxamide (10a). Following general procedure, the compound **10a** was obtained after purification by column chromatography on silica gel (EtOAc:hexane = 20:80) as a pale yellow coloured solid (41 mg, 70%, 0.14 mmol scale); R_f = 0.5 (EtOAc:hexane = 20:80); Mp 167-169 ^oC; IR (DCM): 3342, 2954, 1667, 1515, 1479 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ = 10.29 (s, 1H), 9.23 (dd, 1H, J_1 = 7.6 Hz, J_2 = 1.2 Hz), 8.64 (dd, 1H, J_1 = 4.2 Hz , J_2 = 1.6 Hz), 8.27 (d, 1H, J = 9.2 Hz), 8.24 – 8.19 (m, 3H), 8.15 – 8.07 (m, 4H), 8.02 (t, 1H, J = 7.6 Hz), 7.73 (t, 1H, J = 8.1 Hz), 7.65 (dd, 1H, J_1 = 8.3 Hz, J_2 = 1.2 Hz), 7.43 (dd, 1H, J_1 = 8.3 Hz, J_2 = 4.2 Hz), 3.21 (t, 2H, J = 8.0 Hz), 1.98 – 1.90 (m, 2H), 1.48 – 1.41 (m, 2H), 0.9 (t, 3H, J = 7.3 Hz); ^{13}C NMR (~126 MHz, $CDCl_3$): δ = 168.8, 148.3, 138.5, 137.3, 136.3, 134.6, 132.4, 131.8, 130.9, 130.5, 128.6, 128.3, 128.1, 128.0, 127.5, 127.0, 125.9, 125.7, 125.6, 125.4, 124.4, 124.3, 123.0, 122.1, 121.7, 34.3, 33.9, 22.8, 14.0; HRMS (ESI): *m/z* $[M + H]^+$ calculated for $C_{30}H_{25}N_2O$: 429.1967 found 429.1948.



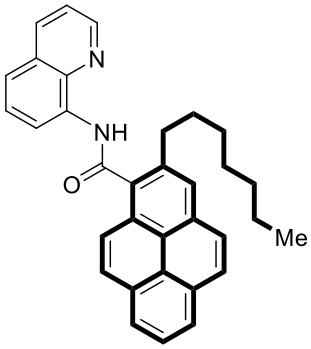
10a

2-Pentyl-*N*-(quinolin-8-yl)pyrene-1-carboxamide (10b). Following general procedure, the compound **10b** was obtained after purification by column chromatography on silica gel (EtOAc:hexane = 20:80) as a pale yellow coloured solid (31 mg, 71%, 0.1 mmol scale); R_f = 0.6 (EtOAc:hexane = 20:80); Mp 148 -150 ^oC; IR (DCM): 3343, 2926, 1669, 1515, 1480 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ = 10.28 (s, 1H), 9.23 (dd, 1H, J_1 = 7.6 Hz, J_2 = 1.1 Hz), 8.64 (dd, 1H, J_1 = 4.2 Hz, J_2 = 1.6 Hz), 8.28 – 8.19 (m, 4H), 8.15 – 8.01 (m, 4H), 8.03 (t, 1H, J = 7.6 Hz), 7.73 (t, 1H, J = 7.8 Hz), 7.64 (dd, 1H, J_1 = 8.3 Hz, J_2 = 1.1 Hz), 7.2 (dd, 1H, J_1 = 8.3 Hz, J_2 = 4.2 Hz), 3.20 (t, 2H, J = 7.8 Hz), 1.97 – 1.92 (m, 2H), 1.42 – 1.28 (m, 4H), 0.82 (t, 3H, J = 7.2 Hz); ^{13}C NMR (~126 MHz, $CDCl_3$): δ = 167.7, 147.3, 137.5, 136.3, 135.3, 133.6, 131.4, 130.8, 129.9, 129.5, 127.5, 127.3, 127.0, 127.0, 126.5, 126.0, 124.9, 124.7, 124.5, 124.4, 123.4, 123.3, 122.0, 121.1, 120.7, 115.8, 33.1, 30.8, 28.7, 21.5, 12.9; HRMS (ESI): *m/z* $[M + H]^+$ calculated for $C_{31}H_{27}N_2O$: 443.2123 found 443.2107.



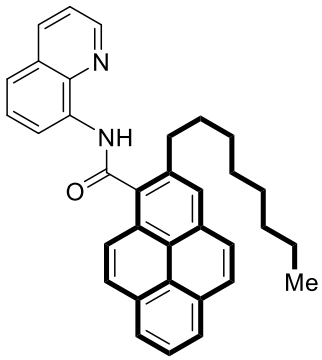
10b

2-Heptyl-*N*-(quinolin-8-yl)pyrene-1-carboxamide (10c). Following general procedure, the compound **10c** was obtained after purification by column chromatography on silica gel (EtOAc:hexane = 10:80) as a pale yellow coloured solid (52 mg, 74%, 0.15 mmol scale); R_f = 0.7 (EtOAc:hexane = 20:80); Mp 108-110 ^oC; IR (DCM): 3346, 2925, 1707, 1673, 1518 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 10.32 (s, 1H), 9.26 (dd, 1H, J_1 = 7.6 Hz, J_2 = 1.2 Hz), 8.63 (dd, 1H, J_1 = 4.2 Hz, J_2 = 1.6 Hz), 8.29 (d, 1H, J = 9.2 Hz), 8.22 – 8.16 (m, 3H), 8.14 – 8.00 (m, 5H), 7.73 (t, 1H, J = 8.1 Hz), 7.63 (dd, 1H, J_1 = 8.3 Hz, J_2 = 1.2 Hz), 7.40 (dd, 1H, J_1 = 8.3 Hz, J_2 = 4.2 Hz), 3.22 (t, 2H, J = 8.0 Hz), 1.98 – 1.92 (m, 2H), 1.46 – 1.38 (m, 2H), 1.32 – 1.25 (m, 2H), 1.22 – 1.16 (m, 4H), 0.8 (t, 3H, J = 6.8 Hz); ^{13}C NMR (~101 MHz, $CDCl_3$): δ = 168.8, 148.3, 138.5, 137.4, 136.3, 134.6, 132.5, 131.8, 131.0, 130.5, 128.6, 128.3, 128.1, 127.5, 127.0, 125.9, 125.8, 125.6, 125.5, 124.5, 124.3, 123.0, 122.2, 121.7, 116.9, 34.2, 32.2, 31.7, 29.7, 29.2, 22.6, 14.1; HRMS (ESI): *m/z* $[M + H]^+$ calculated for $C_{33}H_{31}N_2O$: 471.2436 found 471.2423.



10c

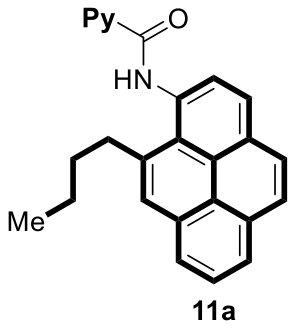
2-Octyl-*N*-(quinolin-8-yl)pyrene-1-carboxamide (10d). Following general procedure, the compound **10d** was obtained after purification by column chromatography on silica gel (EtOAc:hexane = 10:90) as a pale yellow coloured solid (35 mg, 73%, 0.1 mmol scale); R_f = 0.7 (EtOAc:hexane = 20:80); Mp 152-154 ^oC; IR (DCM): 3359, 2932, 1655, 1528, 1475 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6): δ = 10.44 (s, 1H), 8.92 (dd, 1H, J_1 = 7.5 Hz, J_2 = 1.1 Hz), 8.76 (dd, 1H, J_1 = 4.2 Hz, J_2 = 1.6 Hz), 8.48 (dd, 1H, J_1 = 8.3 Hz, J_2 = 1.5 Hz), 8.37 – 8.31 (m, 3H), 8.28 – 8.16 (m, 4H), 8.11 (t, 1H, J = 7.6 Hz), 7.84 (dd, 1H, J_1 = 8.3 Hz, J_2 = 1.1 Hz), 7.79 – 7.75 (m, 1H), 7.62 (dd, 1H, J_1 = 8.2 Hz, J_2 = 4.2 Hz), 3.12 - 308 (m, 2H), 1.86 – 1.82 (m, 2H), 1.34 – 0.97 (m, 10H), 0.71 (t, 3H, J = 7.2 Hz); ^{13}C NMR (~101 MHz, $CDCl_3$): δ = 168.8, 148.3, 138.5, 137.4, 136.3, 134.6, 132.5, 131.8, 131.0, 130.5, 128.6, 128.3, 128.1, 127.5, 127.0, 125.9, 125.8, 125.6, 125.5, 124.5, 124.3, 123.0, 122.1, 121.7, 116.9, 34.2, 32.2, 31.8, 29.7, 29.4, 29.2, 22.6, 14.1; HRMS (ESI): *m/z* $[M + H]^+$ calculated for $C_{34}H_{33}N_2O$: 485.2593 found 485.2571.



10d

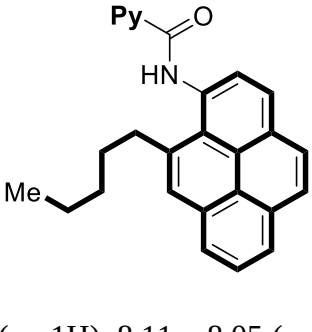
***N*-(10-Butylpyren-1-yl)picolinamide (11a).** Following general procedure, the compound **11a** was obtained after purification by column chromatography on silica gel (EtOAc:hexane = 15:85) as a brown coloured solid (51 mg, 68%);

R_f = 0.6 (EtOAc:hexane = 20:80); Mp 144 – 146 °C; IR (DCM): 3396, 2951, 1678, 1556, 1514 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ = 10.8 (s, 1H), 8.72 (d, 1H, J = 4.3 Hz), 8.53 (d, 1H, J = 8.3 Hz), 8.45 (d, 1H, J = 7.8 Hz), 8.23 (d, 1H, J = 8.3 Hz), 8.16 – 8.13 (m, 1H), 8.08 – 8.03 (m, 3H), 8.01 – 7.96 (m, 2H), 7.91 (s, 1H), 7.56 – 7.53 (m, 1H), 3.48 (t, 2H, J = 7.9 Hz), 1.78 – 1.72 (m, 2H), 1.32 – 1.26 (m, 2H), 0.84 (t, 3H, J = 7.4 Hz); ^{13}C NMR (~101 MHz, $CDCl_3$): δ = 162.5, 150.2, 148.1, 137.7, 136.5, 131.2, 130.9, 130.8, 130.2, 129.8, 127.7, 127.0, 126.8, 126.6, 126.1, 125.7, 125.3, 124.8, 124.7, 124.1, 124.1, 122.7, 38.0, 33.9, 22.7, 13.9; HRMS (ESI): *m/z* [M + H]$^+$ calculated for $C_{26}H_{23}N_2O$: 379.1810 found 379.1794.



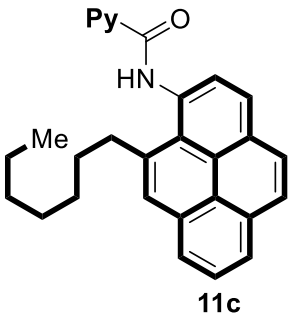
11a

***N*-(10-Pentylpyren-1-yl)picolinamide (11b).** Following general procedure, the compound **11b** was obtained after purification by column chromatography on silica gel (EtOAc:hexane = 20:80) as a brown coloured solid (69 mg, 88%); R_f = 0.5 (EtOAc:hexane = 20:80). Mp 128 – 130 °C; IR (DCM): 3352, 2936, 1686, 1513, 1325 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ = 10.79 (s, 1H), 8.74 – 8.73 (m, 1H), 8.53 (d, 1H, J = 8.3 Hz), 8.46 (d, 1H, J = 7.8 Hz), 8.25 (d, 1H, J = 8.3 Hz), 8.17 – 8.15 (m, 1H), 8.11 – 8.05 (m, 3H), 8.02 – 7.97 (m, 2H), 7.94 (s, 1H), 7.59 – 7.56 (m, 1H), 3.50 (t, 2H, J = 8.0 Hz), 1.80 – 1.76 (m, 2H), 1.28 – 1.22 (m, 4H), 0.78 (t, 3H, J = 6.9 Hz); ^{13}C NMR (~101 MHz, $CDCl_3$): δ = 162.5, 150.2, 148.1, 137.8, 136.6, 131.2, 130.9, 130.8, 130.2, 129.9, 127.8, 127.0, 126.8, 126.6, 126.1, 125.7, 125.4, 124.9, 124.8, 124.2, 124.1, 122.8, 38.4, 31.8, 31.6, 22.6, 14.1; HRMS (ESI): *m/z* [M + H]$^+$ calculated for $C_{27}H_{25}N_2O$: 393.1967 found 393.1957.



11b

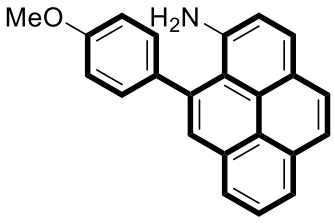
***N*-(10-Heptylpyren-1-yl)picolinamide (11c).** Following general procedure, the compound **11c** was obtained after purification by column chromatography on silica gel (EtOAc:hexane = 20:80) as a brown coloured solid (48 mg, 58%); R_f = 0.6 (EtOAc:hexane = 20:80). Mp 132 – 134 °C; IR (DCM): 3375, 2928, 1690, 1517, 1321cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ = 10.77 (s, 1H), 8.73 (d, 1H, J = 4.6 Hz), 8.52 (d, 1H, J = 8.2 Hz), 8.46 (d, 1H, J = 7.8 Hz), 8.24 (d, 1H, J = 8.2 Hz), 8.15 (d, 1H, J = 7.5 Hz), 8.09 – 8.06 (m, 3H), 8.01 - 7.97 (m, 2H), 7.92 (s, 1H), 7.58 – 7.55 (m, 1H), 3.48 (t, 2H, J = 7.8 Hz), 1.78 – 1.74 (m, 2H), 1.22 – 1.13 (m, 8H), 0.84 (t, 3H, J = 7.1 Hz); ^{13}C NMR (~101 MHz, $CDCl_3$): δ = 162.5, 150.2, 148.1, 137.8, 136.6, 131.2, 130.9, 130.8,



11c

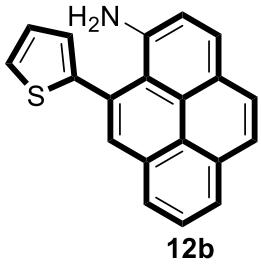
130.2, 129.9, 127.8, 127.0, 126.8, 126.6, 126.1, 125.7, 125.4, 124.8, 124.8, 124.1, 124.1, 122.8, 38.4, 31.9, 31.9, 29.7, 29.2, 22.6, 14.1; HRMS (ESI): *m/z* $[M + H]^+$ calculated for $C_{29}H_{29}N_2O$: 421.2280 found 421.2265.

10-(4-Methoxyphenyl)pyren-1-amine (12a). Following general procedure, the compound **12a** was obtained after purification by column chromatography on silica gel (EtOAc:hexane = 5:95) as a brown coloured solid (27 mg, 56%, 0.15 mmol scale); R_f = 0.8 (EtOAc:hexane = 20:80); Mp 134 – 136 °C; IR (DCM): 3484, 3386, 1601, 1510, 1450 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ = 8.07 – 7.91 (m, 5H), 7.84 (d, 1H, *J* = 8.7 Hz), 7.72 (s, 1H), 7.54 (d, 2H, *J* = 7.9 Hz), 7.23 (d, 1H, *J* = 8.2 Hz), 7.07 (d, 2H, *J* = 7.9 Hz), 3.94 (s, 3H). (The NH_2 signal could not be clearly located in the proton NMR spectrum); ^{13}C NMR (~101 MHz, $CDCl_3$): δ = 159.2, 142.8, 137.1, 135.6, 132.4, 131.2, 130.3, 129.1, 128.0, 127.4, 127.1, 126.2, 125.2, 124.2, 123.8, 123.3, 122.8, 115.9, 114.5, 113.9, 55.4; HRMS (ESI): *m/z* $[M + H]^+$ calculated for $C_{23}H_{18}NO$: 324.1388 found 324.1373.



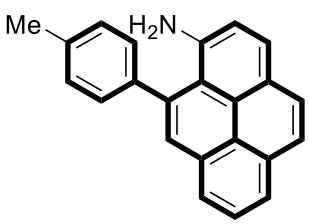
12a

10-(Thiophen-2-yl)pyren-1-amine (12b). Following general procedure, the compound **12b** was obtained after purification by column chromatography on silica gel (EtOAc:hexane = 5:95) as a brown coloured solid (25 mg, 70%, 0.12 mmol scale); R_f = 0.8 (EtOAc:hexane = 20:80); Mp 169 – 171 °C; IR (DCM): 3471, 3398, 2928, 1617, 1452 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ = 8.07 (d, 1H, *J* = 7.3 Hz), 8.02 (d, 1H, *J* = 8.2 Hz), 7.97 – 7.91 (m, 4H), 7.83 (d, 1H, *J* = 8.8 Hz), 7.52 (d, 1H, *J* = 5.2 Hz), 7.28 – 7.26 (m, 2H), 7.22 – 7.20 (m, 1H), 4.25 (br s, 2H); ^{13}C NMR (~101 MHz, $CDCl_3$): δ = 144.3, 143.0, 132.4, 131.2, 130.7, 129.1, 128.0, 127.6, 127.3, 127.1, 126.3, 126.2, 125.6, 124.4, 124.0, 123.2, 123.0, 116.2, 114.5; HRMS (ESI): *m/z* $[M + H]^+$ calculated for $C_{20}H_{14}NS$: 300.0847 found 300.0844.



12b

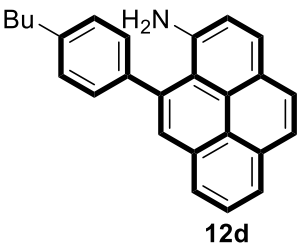
10-(*p*-Tolyl)pyren-1-amine (12c). Following general procedure, the compound **12c** was obtained after purification by column chromatography on silica gel (EtOAc:hexane = 5:95) as a red coloured solid (112 mg, 73%, 0.5 mmol); R_f = 0.9 (EtOAc:hexane = 20:80); Mp 150 – 152 °C; IR (DCM): 3494, 3398, 1617, 1513, 1452 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ = 8.07 – 7.93 (m, 5H), 7.87 – 7.84 (m, 1H), 7.73 – 7.72 (m, 1H), 7.53 – 7.51 (m, 2H), 7.37 – 7.35 (m, 2H), 7.23 (d, 1H, *J* =



12c

8.0 Hz), 4.13 (br s, 2H), 2.53 (s, 3H); ^{13}C NMR (~101 MHz, $CDCl_3$): δ = 143.0, 140.5, 137.5, 132.4, 131.3, 129.2, 129.1, 128.9, 128.0, 127.4, 127.1, 126.2, 125.3, 124.1, 123.8, 123.2, 122.8, 115.9, 114.3, 21.4; HRMS (ESI): *m/z* $[M + H]^+$ calculated for $C_{23}H_{18}N$: 308.1439 found 308.1428.

10-(4-Butylphenyl)pyren-1-amine (12d). The compound **12d** was obtained *via* a one-pot sequential C-H arylation of **2b** under standard reaction conditions and neat condition, followed by NaOH-mediated hydrolysis procedure. After the standard work-up procedure and purification by column chromatography on silica gel (EtOAc:hexane = 5:95) as a red coloured solid (32 mg, 46%, 0.2 mmol scale from **2b**); R_f = 0.9 (EtOAc:hexane = 20:80); Mp 142 – 144 ^{o}C. IR (DCM): 3490, 3394, 1613, 1513, 1421 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.06 – 8.01 (m, 2H), 8.00 – 7.90 (m, 3H), 7.83 (d, 1H, *J* = 8.8 Hz), 7.72 (s, 1H), 7.53 (d, 2H, *J* = 8.0 Hz), 7.36 (d, 2H, *J* = 8.0 Hz), 7.23 (d, 1H, *J* = 8.2 Hz), 4.13 (s, 2H), 2.77 (t, 2H, *J* = 7.8 Hz), 1.77 – 1.70 (m, 2H), 1.50 – 1.44 (m, 2H), 1.02 (t, 3H, *J* = 7.4 Hz); ^{13}C NMR (~101 MHz, $CDCl_3$): δ = 143.0, 142.5, 140.7, 137.5, 132.4, 131.2, 129.0, 128.9, 128.5, 128.0, 127.4, 127.1, 126.2, 125.3, 124.1, 123.7, 123.2, 122.8, 115.8, 114.3, 35.5, 33.7, 22.5, 14.1; HRMS (ESI): *m/z* $[M + H]^+$ calculated for $C_{26}H_{24}N$: 350.1909 found 350.1897.



12d

References :

1. Zaitsev, V. G.; Shabashov, D.; Daugulis, O. *J. Am. Chem. Soc*. **2005**, *127*, 13154.

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

3. (a) Fahey, D. R. *J. Organomet. Chem*. **1971**, *27*, 283. (b) Fahey, D. R. *J. Chem. Soc. D* **1970**, 417a.

4. Jordan, R. F.; Taylor, D. F. *J. Am. Chem. Soc.* **1989**, *111*, 778.

5. Moor, E. J.; Pretzer, W. R.; O'Connell, T. J.; Harris, J.; LaBounty, L.; Chou, L.; Grimmer, S. S. *J. Am. Chem. Soc.* **1992**, *114*, 5888.

6. Murai, S.; Kakiuchi, F.; Sekine, S.; Tanaka, Y.; Kamatani, A.; Sonoda, M.; Chatani, N. *Nature* **1993**, *366*, 529.

7. (a) Zhang, Y.-H.; Shi, G.-F.; Yu, J.-Q. Carbon–Carbon σ-Bond Formation *via* C–H Bond Functionalization, In Comprehensive Organic Synthesis II, Chap. 3.23; Knochel, P., Ed.; Elsevier: Amsterdam, **2014**, 1101. (b) For a themed issue on C–H activation, see: Crabtree, R. H.; Lei, A. *Chem. Rev*. **2017**, *117*, 8481. (c) For a themed issue on C–H activation reactions,

see: Davies, H. M. L.; Bois, J.; Yu, J.-Q. *Chem. Soc. Rev*. **2011**, *40*, 1855. (d) Kakiuchi, F.; Murai, S. *Acc. Chem. Res*. **2002**, *35*, 826. (e) Hirano, K.; Miura, M. Chem. Lett. 2015, 44, 868. (f) Rej, S.; Das, A.; Chatani, N. *Coord. Chem. Rev*. **2021**, *431*, 213683. (g) Colby, D. A.; Bergman, R. G.; Ellman, J. A. *Chem. Rev*. **2010**, *110*, 624. (h) Lyons, T. W.; Sanford, M. S. *Chem. Rev*. **2010**, *110*, 1147. (i) Nguyen, T. H. L.; Gigant, N.; Joseph, D. *ACS Catal*. **2018**, *8*, 1546. (j) Moselage, M.; Li, J.; Ackermann, L. *ACS Catal*. **2016**, *6*, 498. (k) Zhu, R.-Y.; Farmer, M. E.; Chen, Y.-Q.; Yu, J.-Q. *Angew. Chem. Int. Ed*. **2016**, *55*, 10578.

8. (a) Yoshikai, N. J. *Synth. Org. Chem. Jpn.* **2014**, *72*, 1198. (b) Huang, Z.; Lim, H. N.; Mo, F.; Young, M. C.; Dong, G. *Chem. Soc. Rev*. **2015**, *44*, 7764. (c) Rao, W.-H.; Shi, B.-F. *Org. Chem. Front*. **2016**, *3*, 1028. (d) Gensch, T.; Hopkinson, M. N.; Glorius, F.; Wencel-Delord, J. *Chem. Soc. Rev*. **2016**, *45*, 2900. (e) Yoshino, T.; Matsunaga, S. *Adv. Synth. Catal*. **2017**, *359*, 1245. (f) Wang, W.; Lorion, M. M.; Shah, J.; Kapdi, A. R.; Ackermann, L. *Angew. Chem. Int. Ed.* **2018**, *57*, 14700. (g) Banerjee, A.; Sarkar, S.; Patel, B. *Org. Biomol. Chem*. **2017**, *15*, 505. (h) Bag, S.; Maiti, D. *Synthesis* **2016**, *48*, 804. (i) Baudoin, O. *Acc. Chem. Res*. **2017**, *50*, 1114. (j) Yang, K.; Song, M.; Liu, H.; Ge, H. *Chem. Sci*. **2020**, *11*, 12616. (k) Subramanian, P.; Rudolf, G. C.; Kaliappan, K. P. *Chem. Asian J*. **2016**, *11*, 168. (l) Zhang, M.; Luo, A.; Shi, Y.; Su, R.; Yang, Y.; You, J. *ACS Catal*. **2019**, *9*, 11802. (m) Yorimitsu, H.; Yoshimura, A.; Misaki, Y. *Synthesis* **2020**, *52*, 3326. (n) Saito, H.; Yamamoto, K.; Sumiya, Y.; Liu, L.-J.; Nogi, K.; Maeda, S.; Yorimitsu, H. *Chem. Asian J*. **2020**, *15*, 2442.

9. For selected reviews dealing with the bidentate directing group (DG)-aided C–H functionalization/arylation, see: (a) Daugulis, O.; Roane, J.; Tran, L. D. *Acc. Chem. Res*. **2015**, *48*, 1053. (b) Rej, S.; Ano, Y.; Chatani, N. *Chem. Rev*. **2020**, *120*, 1788. (c) Rouquet, G.; Chatani, N. *Angew. Chem. Int. Ed*. **2013**, *52*, 11726. (d) Yang, X.; Shan, G.; Wang, L.; Rao, Y. *Tetrahedron Lett*. **2016**, *57*, 819. (e) Li, H.; Li, B.-J.; Shi, Z.-J. *Catal. Sci. Technol*. **2011**, *1*, 191. (f) Castro, L. C. M.; Chatani, N. *Chem. Lett*. **2015**, *44*, 410. (g) Yadav, M. R.; Rit, R. K.; Majji, S.; Sahoo, A. K. *Asian J. Org. Chem*. **2015**, *4*, 846. (h) Sambiagio, C.; Schönbauer, D.; Blieck, R.; Dao-Huy, T.; Pototschnig, G.; Schaaf, P.; Wiesinger, T.; Zia, M. F.; WencelDelord, J.; Besset, T.; Maes, B. U. W.; Schnürch, M. *Chem. Soc. Rev*. **2018**, *47*, 6603. (i) He, G.; Wang, B.; Nack, W. A.; Chen, G. *Acc. Chem. Res*. **2016**, *49*, 635. (j) Noisier, A. F. M.; Brimble, M. A. *Chem. Rev*. **2014**, *114*, 8775.

10. (a) Yoshikai, N. *J. Synth. Org. Chem. Jpn.* **2014**, *72*, 1198. (b) Huang, Z.; Lim, H. N.; Mo, F.; Young, M. C.; Dong, G. *Chem. Soc. Rev.* **2015**, *44*, 7764. (c) Rao, W.-H.; Shi, B.-F. *Org. Chem. Front.* **2016**, *3*, 1028. (d) Gensch, T.; Hopkinson, M. N.; Glorius, F. Wencel-Delord, J. *Chem. Soc. Rev.* **2016**, *45*, 2900. (e) Yoshino, T.; Matsunaga, S. *Adv. Synth. Catal.* **2017**, *359*,

1245. (f) Wang, W.; Lorion, M. M.; Shah, J.; Kapdi, A. R.; Ackermann, L. *Angew. Chem. Int. Ed.* **2018**, *57*, 14700. (g) Banerjee, A.; Sarkar S.; Patel, B. *Org. Biomol. Chem.* **2017**, *15*, 505. (h) Bag S.; Maiti, D. *Synthesis* **2016**, *48*, 804. (i) Baudoin, O. *Acc. Chem. Res.* **2017**, *50*, 1114. (j) Yang, K.; Song, M.; Liu, H.; Ge, H. *Chem. Sci.* **2020**, *11*, 12616. (k) Subramanian, P.; Rudolf, G. C.; Kaliappan, K. P. *Chem. Asian J.* **2016**, *11*, 168. (l) Zhang, M.; Luo, A.; Shi, Y.; Su, R.; Yang, Y.; You, J. *ACS Catal.* **2019**, *9*, 11802. (m) Yorimitsu, H.; Yoshimura, A.; Misaki, Y. *Synthesis* **2020**, *52*, 3326. (n) Saito, H.; Yamamoto, K.; Sumiya, Y.; Liu, L.-J.; Nogi, K.; Maeda, S.; Yorimitsu, H. *Chem. Asian J.* **2020**, *15*, 2442.

11. For selected reviews dealing with the bidentate directing group (DG)-aided C-H functionalization/arylation, see: (a) Daugulis, O.; Roane, J.; Tran, L. D. *Acc. Chem. Res.* **2015**, *48*, 1053. (b) Rej, S.; Ano, Y.; Chatani, N. *Chem. Rev.* **2020**, *120*, 1788. (c) Rouquet G.; Chatani, N. *Angew. Chem. Int. Ed.* **2013**, *52*, 11726. (d) Yang, X.; Shan, G.; Wang, L.; Rao, Y. *Tetrahedron. Lett*. **2016**, *57*, 819. (e) Li, H.; Li, B.-J.; Shi, Z.-J. *Catal. Sci. Technol.* **2011**, *1*, 191. (f) Castro, L. C. M.; Chatani, N. *Chem. Lett*. **2015**, *44*, 410. (g) Yadav, M. R.; Rit, R. K.; Majji, S.; Sahoo, A. K. *Asian. J. Org. Chem.* **2015**, *4*, 846. (h) Sambiagio, C.; Schönbauer, D.; Blieck, R.; Dao-Huy, T.; Pototschnig, G.; Schaaf, P.; Wiesinger, T.; Zia, M. F.; Wencel-Delord, J.; Besset, T.; Maes, B. U. W.; Schnürch, M. *Chem. Soc. Rev.* **2018**, 47, 6603. (i) He, G.; Wang, B.; Nack W. A.; Chen, G. *Acc. Chem. Res.* **2016**, *49*, 635; (j) Noisier, A. F. M.; Brimble, M. A. *Chem. Rev.* **2014**, *114*, 8775.

12. For selected papers dealing with 8-aminoquinoline-aided C-H functionalization, see: (a) Shabashov, D.; Daugulis, O. *J. Am. Chem. Soc.* **2010**, *132*, 3965. (b) Aihara, Y.; Chatani, N. *J. Am. Chem. Soc.* **2014**, *136*, 898. (c) Takamatsu, K.; Hirano, K.; Miura, M. *Angew. Chem. Int. Ed.* **2017**, *56*, 5353. (d) Kanyiva, K. S.; Kuninobu,Y.; Kanai, M. *Org. Lett.* **2014**, *16*, 1968. (e) Reddy, M. D.; Blanton, A. N.; Watkins, E. B. *J. Org. Chem.* **2017**, *82*, 5080. (f) Chen, Y.; Quan, Y.; Xie, Z. *Chem. Commun.* **2020**, *56*, 12997. (g) Gou, Q.; Zhang, Z.-F.; Liu, Z.-C.; Qin, J. *J. Org. Chem.* **2015**, *80*, 3176. (h) Reddy, B. V. S.; Reddy, L. R.; Corey, E. J. *Org. Lett.* **2006**, *8*, 3391. (i) Hu, P.; Bach, T. *Synlett* **2015**, *26*, 2853. (j) Hoshiya, N.; Kondo, M.; Fukuda, H.; Arisawa, M.; Uenishi J.; Shuto, S. *J. Org. Chem.* **2017**, *82*, 2535.

13. For selected papers dealing with picolinamide-aided C-H functionalization, see: (a) Zaitsev, V. G.; Shabashov, D.; Daugulis, O. *J. Am. Chem. Soc.* **2005**, *127*, 13154. (b) Xu, J.-W.; Zhang, Z.-Z.; Rao, W.-H.; Shi, B.-F. *J. Am. Chem. Soc.* **2016**, *138*, 10750; (c) Bolsakova, J.; Lukasevics, L.; Grigorijeva, L. *J. Org. Chem.* **2020**, *85*, 4482. (d) He, G.; Chen, G. *Angew. Chem. Int. Ed.* **2011**, *50*, 5192. (e) Zeng, W.; Nukeyeva, M.; Wang, Q.; Jiang, C. *Org. Biomol. Chem.* **2018**, *16*, 598. (f) Zhao, Y.; Chen, G. *Org. Lett.* **2011**, *13*, 4850.

14. For selected articles of our group dealing with bidentate DG-aided C-H functionalization, see: (a) Parella, R.; Babu, S. A. *J. Org. Chem.* **2017**, *82*, 7123; (b) Gopalakrishnan, B.; Mohan, S.; Parella, R.; Babu, S. A. *J. Org. Chem.* **2016**, *81*, 8988; (c) Gopalakrishnan, B.; Babu, S. A.; Padmavathi, R. *Tetrahedron* **2015**, *71*, 8333; (d) Reddy, C.; Bisht, N.; Parella, R.; Babu, S. A. *J. Org. Chem.* **2016**, *81*, 12143; (e) Parella, R.; Babu, S. A. *J. Org. Chem.* **2017**, *82*, 6550. (f) Naveen, Rajkumar, V.; Babu, S. A. Gopalakrishnan, B. *J. Org. Chem.* **2016**, *81*, 12197. (g) Parella, R.; Babu, S. A. *J. Org. Chem.* **2015**, *80*, 12379. (h) Parella, R.; Babu, S. A. *J. Org. Chem.* **2015**, *80*, 2339. (i) Singh, P.; Babu, S. A.; Aggarwal, Y.; Patel, P. *Asian J. Org. Chem.* **2021**, *10*, 180. (j) Bisht, N.; Babu, S. A.; Tomar, R. *Asian J. Org. Chem.* **2020**, *9*, 1225. (k) Padmavathi, R.; Babu, S. A. *Asian J. Org. Chem.* **2019**, *8*, 899. (l) Singh, P.; Dalal, A.; Babu, S. A. *Asian J. Org. Chem.* **2019**, *8*, 877.

15. Available reports dealing with single examples directing group-aided C-H functionalization of pyrene core (Scheme 1), see: (a) Rej, S.; Chatani, N. *ACS Catal.* **2018**, *8*, 6699. (b) Odani, R.; Hirano, K.; Satoh, T.; Miura, M. *J. Org. Chem.* **2013**, *78*, 11045. (c) Pradhan, S.; De, B. P.; Punniyamurthy, T. *J. Org. Chem.* **2017**, *82*, 4883. (d) Roy, S.; Pradhan, S.; Punniyamurthy, T. *Chem. Commun.* **2018**, *54*, 3899. (e) Iwasaki, M.; Kaneshika, W.; Tsuchiya, Y.; Nakajima, K.; Nishihara, Y.; *J. Org. Chem.* **2014**, *79*, 11330. (f) Ying, J.; Fu, L.-Y.; Zhong, G.; Wu, X.-F. *Org. Lett.* **2019**, *21*, 5694. (g) Asako, S.; Ilies, L.; Nakamura, E. *J. Am. Chem. Soc.* **2013**, *135*, 17755. (h) Pradhan, S.; Roy, S.; Banerjee, S.; De, P. B.; Punniyamurthy, T. *J. Org. Chem.* **2020**, *85*, 5741. (i) Gao, Y.; Zhang, M.; Wang, C.; Yang, Z.; Huang, X.; Feng, R.; Qi, C.; *Chem. Commun.* **2020**, *56*, 14231. (j) During our investigation of this work, a paper revealing the Pd-catalyzed arylation of pyrene 1-carboxylic acid followed by decarboxylation appeared, Just-Baringo, X.; Shin, Y.; Panigrahi, A.; Zarattini, M.; Nagyte, V.; Zhao, L.; Kostarelos, K.; Casiraghi, C.; Larrosa, I. *Chem. Sci.* **2020**, *11*, 2472. (k) During our investigation of this work, a paper revealing an example of Cu-catalyzed arylation of pyrene 1-carboxamide by using For a paper revealing an example of Cu-catalyzed C(9)-H arylation of pyrene-1-carboxamide with aryliodonium salts as arylating reagent, see: Luo, A.; Zhang, M.; Fu, Z.; Lan, J.; Wu, D.; You, J. *Beilstein. J. Org. Chem.* **2020**, *16*, 530.

16. Selected reviews dealing with synthesis and application of pyrene motifs, see: (a) Mateo-Alonso, A. *Eur. J. Org. Chem.* **2017**, 7006. (b) Feng, X.; Hu, J.-Y.; Redshaw, C.; Yamato, T. *Chem. Eur. J.* **2016**, *22*, 11898. (c) Zych, D. *Molecules* **2019**, *24*, 2551. (d) Figueira-Duarte, T. M.; Müllen, K. *Chem. Rev.* **2011**, *111*, 7260. (e) Ohishi, Y.; Inouye, M. *Tetrahedron Lett.* **2019**, *60*, 151232. (f) Howarth, A. J.; Majewski, M. B.; Wolf, M. O. *Coord. Chem. Rev.* **2015**, *282-283*, 139. (g) Mateo-Alonso, A. *Chem. Soc. Rev.* **2014**, *43*, 6311. (h) Karuppannan, S.;

Chambron, J.-C. *Chem. Asian. J.* **2011**, *6*, 694. (i) Gong, Y.; Zhan, X.; Li, Q.; Li, Z. *Sci. China Chem.* **2016**, *59*, 1623. (j) Bains, G.; Patel, A. B.; Narayanaswami, V. *Molecules* **2011**, *16*, 7909. (k) Pirouz, S.; Duhamel, J. *J. Polym. Sci., Part B: Polym. Phys.* **2017**, *55*, 7. (l) Manandhar, E.; Wallace, K. J. *Inorg. Chim. Acta* **2012**, *381*, 15. (m) Islam, M. M.; Hu, Z.; Wang, Q.; Redshaw, C.; Feng, X. *Mater. Chem. Front.* **2019**, *3*, 762; (n) Casas-Solvas, J. M.; Howgego, J. D.; Davis, A. P. *Org. Biomol. Chem.* **2014**, *12*, 212.

17. Coventry, D. N.; Batsanov, A. S.; Goeta, A. E.; Howard, J. K.; Marder, T. B.; Perutz, R. N. *Chem. Commun.* **2005**, 2172. (b) Tchon, D.; Trzybinski, Wrona-Piotrowicz, A. Makal, A. *CrystEngComm* **2019**, *21*, 5845. (c) Picchiotti, A.; Nenov, A.; Giussani, A.; Prokhorenko, V. I.; Miller, R. J. D.; Mukamel, S.; Garavelli, M. *J. Phys. Chem. Lett.* **2019**, *10*, 3481. (d) Anetai, H.; Wada, Y.; Takeda, T.; Hoshino, N.; Yamamoto, S.; Mitsuishi, M.; Takenobu, T.; Akutagawa, T. *J. Phys. Chem. Lett.* **2015**, *6*, 1813. (e) Seki, H.; Onishi, S.; Asamura, N.; Suzuki, Y.; Kawamata, J.; Kaneno, D.; Hadano, S.; Watanabe, S.; Niko, Y. *J. Mater. Chem. B* **2018**, *6*, 7396. (f) Nakamura, Y.; Nakazato, T.; Kamatsuka, T.; Shinokubo, H.; Miyake, Y. *Chem. Eur. J.* **2019**, *25*, 10571. (g) Merz, J.; Fink, J.; Friedrich, A.; Krummenacher, I.; Mamari, H. H. A.; Lorenzen, S.; Haehnel, M.; Eichhorn, A.; Moos, M.; Holzapfel, M. Braunschwieg, H.; Lambert, C.; Steffen, A. Ji, L.; Marder, T. B. *Chem. Eur. J.* **2017**, *23*, 13164. (h) Shao, J.-Y.; Yang, N.; Guo, W.; Cui, B.-B.; Chen, Q.; Zhong, Y.-W. *Chem. Commun.* **2019**, *55*, 13406. (i) Takaishi, K.; Takehana, R.; Ema, T. *Chem. Commun.* **2018**, *54*, 1449. (j) Liu, M.; Gong, X.; Zheng, C.; Gao, D. *Asian J. Org. Chem.* **2017**, *6*, 1903. (k) Yang, W.; Monteiro, J. H. S. K.; de Bettencourt-Dias, A.; Catalano, V. J.; Chalifoux, W. A. *Angew. Chem. Int. Ed.* **2016**, *55*, 10427. (l) Matsumoto, A.; Suzuki, M.; Hayashi, H.; Kuzuhara, D.; Yuasa, J.; Kawai, T.; Aratani, N.; Yamada, H.; *Bull. Chem. Soc. Jpn.* **2017**, *90*, 667. (m) Hogan, D. T.; Gelfand, B. S.; Spasyuk, D. M.; Sutherland, T. C. *Mater. Chem. Front.* **2020**, *4*, 268.

18. Yang, J.; Huang, J.; Sun, N.; Peng, Q.; Li, Q.; Ma, D.; Li, Z. *Chem. Eur. J.* **2015**, *21*, 6862. (b) Yang, J.; Guo, Q.; Wen, X.; Gao, X.; Peng, Q.; Li, Q.; Ma, D.; Li, Z. *J. Mater. Chem. C* **2016**, *4*, 8506. (c) Thomas, K. R.; Lin, J. T.; Tao, Y.-T.; Ko, C.-W. *J. Am. Chem. Soc.* **2001**, *123*, 9404. (d) Burroughes, J. H.; Bradley, D. D. C.; Brown, A. R.; Marks, R. N.; Mackay, K.; Friend, R. H.; Burns, P. L.; Holmes, A. B. *Nature* **1990**, *347*, 539. (e) Bartelmess, J.; Ballesteros, B.; de la Torre, G.; Kiessling, D.; Campidelli, S.; Prato, M.; Torres, T.; Guldi, D. M. *J. Am. Chem. Soc.* **2010**, *132*, 16202. (f) Buene, A. F.; Ose, E. E.; Zakariassen, A. G.; Hagfeldt, A.; Hoff, B. H. *J. Mater. Chem. A* **2019**, *7*, 7581. (g) Chang, J.; Lee, C.-P.; Kumar, D.; Chen, P.-W.; Lin, L.-Y.; Thomas, K. R. J.; Ho, C. *J. Power Sources* **2013**, *240*, 779. (h) Lee, O. P.; Yiu, A. T.; Beauguge, P. M.; Woo, C. H.; Holcombe, T. W.; Millstone, J. E.;

Douglas, J. D.; Chen, M. S.; Fréchet, J. M. J. *Adv. Mater.* **2011**, *23*, 5359. (i) Zhao, Z.; Lam, J. W.; Tang, B. Z. *J. Mater. Chem.* **2012**, *22*, 23726. (j) Tao, S.; Zhou, Y.; Lee, C.-S.; Zhang, X.; Lee, S.-T. *Chem. Mater.* **2010**, *22*, 2138. (k) Hong, Y.; Lam, J. W. Y.; Tang, B. Z. *Chem. Soc. Rev.* **2011**, *40*, 5361. (l) Moulin, E.; Busseron, E.; Giuseppone, N. Supramolecular Materials for Opto-Electronics, Koch, N. (Ed.), Royal Society of Chemistry, Cambridge, 2015, pp. 1 – 52. (m) Zhang, M.; Parajuli, R. R.; Mastrogiovanni, D.; Dai, B.; Lo, P.; Cheung, W.; Brukh, R.; Chiu, P. L.; Zhou, T.; Liu, Z.; Garfunkel, E.; He, H. *Small* **2010**, *6*, 1100. (n) Yu, C.-C.; Jiang, K.-J.; Huang, J.-H.; Zhang, F.; Bao, X.; Wang, F.-W.; Yang, L.-M.; Song, Y. *Org. Electron.* **2013**, *14*, 445.

19. (a) Niko, Y.; Kawauchi, S.; Otsu, S.; Tokumaru, K.; Konishi, G.-i. *J. Org. Chem.* **2013**, *78*, 3196. (b) Kim, C.; Yoon, J.-Y.; Lee, S. J.; Lee, H. W.; Kim, Y. K.; Yoon, S. S. *J. Nanosci. Nanotechnol.* **2015**, *15*, 5246. (c) Zhang, R.; Zhao, Y.; Zhang, T.; Xu, L.; Ni, Z. *Dyes Pigments* **2016**, *130*, 106. (d) Zhang, R.; Zhang, T.; Xu, L.; Han, F.; Zhao, Y.; Ni, Z. *J. Mol. Struct.* **2017**, *1127*, 237. (e) Gong, X.; Zheng, C.; Feng, X.; Huan, Y.; Li, J.; Yi, M.; Fu, Z.; Huang, W.; Gao, D. *Chem. Asian J.* **2018**, *13*, 3920. (f) Li, D.; Shao, J.-Y.; Li, Y.; Li, Y.; Deng, L.-Y.; Zhong, Y.-W.; Meng, Q. *Chem. Commun.* **2018**, *54*, 1651.

20. CCDC 2068244 (**4a**), CCDC 2068245 (**4e**), CCDC 2068246 (**5n**), and CCDC 2068247 (**12c**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* www.ccdc.cam.ac.uk/data_request/cif.

Chapter 5

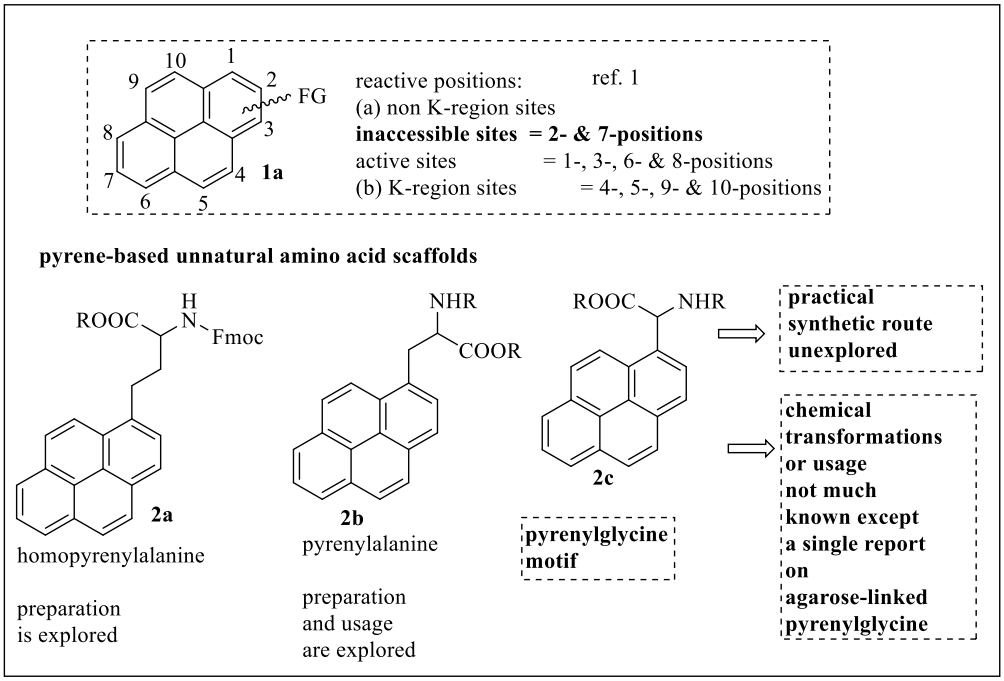
Picolinamide-assisted *ortho*-C-H functionalization of pyrenylglycine derivatives using aryl iodides

For the purpose of this Thesis work, the work of Chapter 5 is re-used (adapted) with permission from **Dalal, A**.; Bodak, S.; Babu, S. A.* *Org. Biomol. Chem.* **2024**, *22*, 1279. *(*Title: Picolinamide-assisted *ortho*-C-H functionalization of pyrenylglycine derivatives using aryl iodides).

Pyrene is a notorious chromophore and its fluorescence properties have been extensively utilized in various branches of chemical, materials, and biological sciences to study the fundamental and applied photochemical research topics.[1,2] Pyrene-based organic materials and polymers are active components in electronic and optoelectronic devices.[1,2]

Unnatural amino acid motifs have received a vast amount of attention in organic synthesis, medicinal chemistry, and chemical biology.[3,4] Unnatural amino acids are building blocks to synthesize drugs, biologically active peptides, and tools to study the functions of peptides. The incorporation of unnatural amino acids into peptides is found to enhance the performance of peptides and the proteolytic stability of peptides.[3,4] Given their applications across branches of chemical sciences and demand, there have been constant efforts in designing several classes of unnatural amino acid derivatives.[3,4]

Given the useful photophysical properties of the pyrene motif, its incorporation in small organic molecules and peptides has been achieved using the functional groups present in pyrene motifs.[1,2,5-9] The incorporation of pyrene unit in peptides is generally done at the side chain or N or C terminals and independently, pyrenes have been used as a tool to detect and study the functions of amino acids and peptides.[5,6] The availability of pyrene-based unnatural amino acid motifs is highly useful as it can be directly incorporated into the peptide backbone.[7,8] Along this line, the construction of pyrenylalanine (pyrene-based alanine unnatural amino acid) scaffolds and their usage are known in the literature (Scheme 1).[8] On the other hand, the chemical transformations involving pyrenylglycine unnatural amino acid motifs and practical methods affording pyrenylglycine derivatives are less explored.[9] There exists only a single report which dealt with the synthesis of two examples of agarose-linked pyrenylglycine derivative *via* the Petasis-Ugi multicomponent reaction and tested them as the targets for the enrichment of phosphorylated peptides.[9]

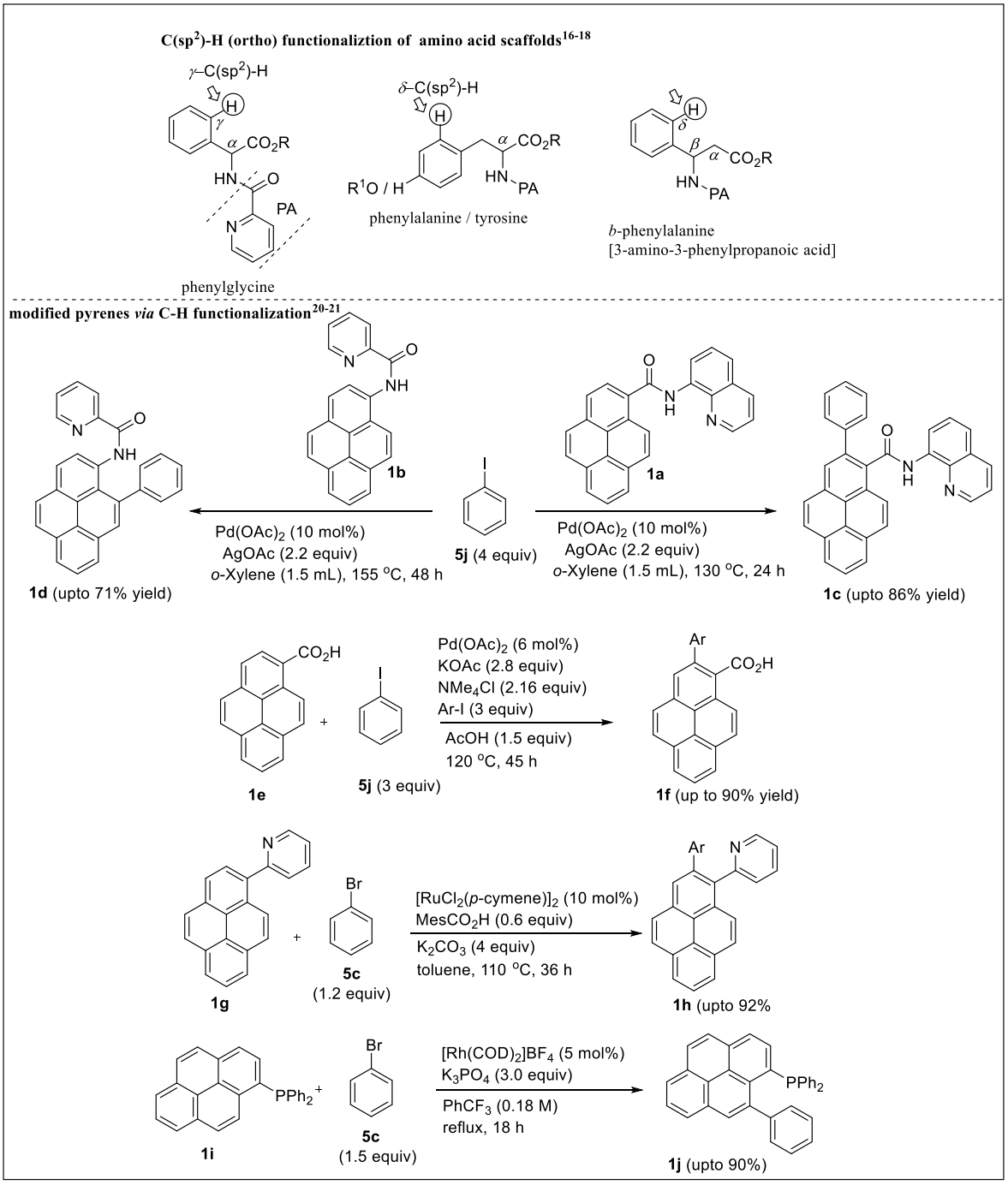


Scheme 1. Pyrene-based unnatural amino acid motifs and reactive positions in pyrene toward its functionalization.

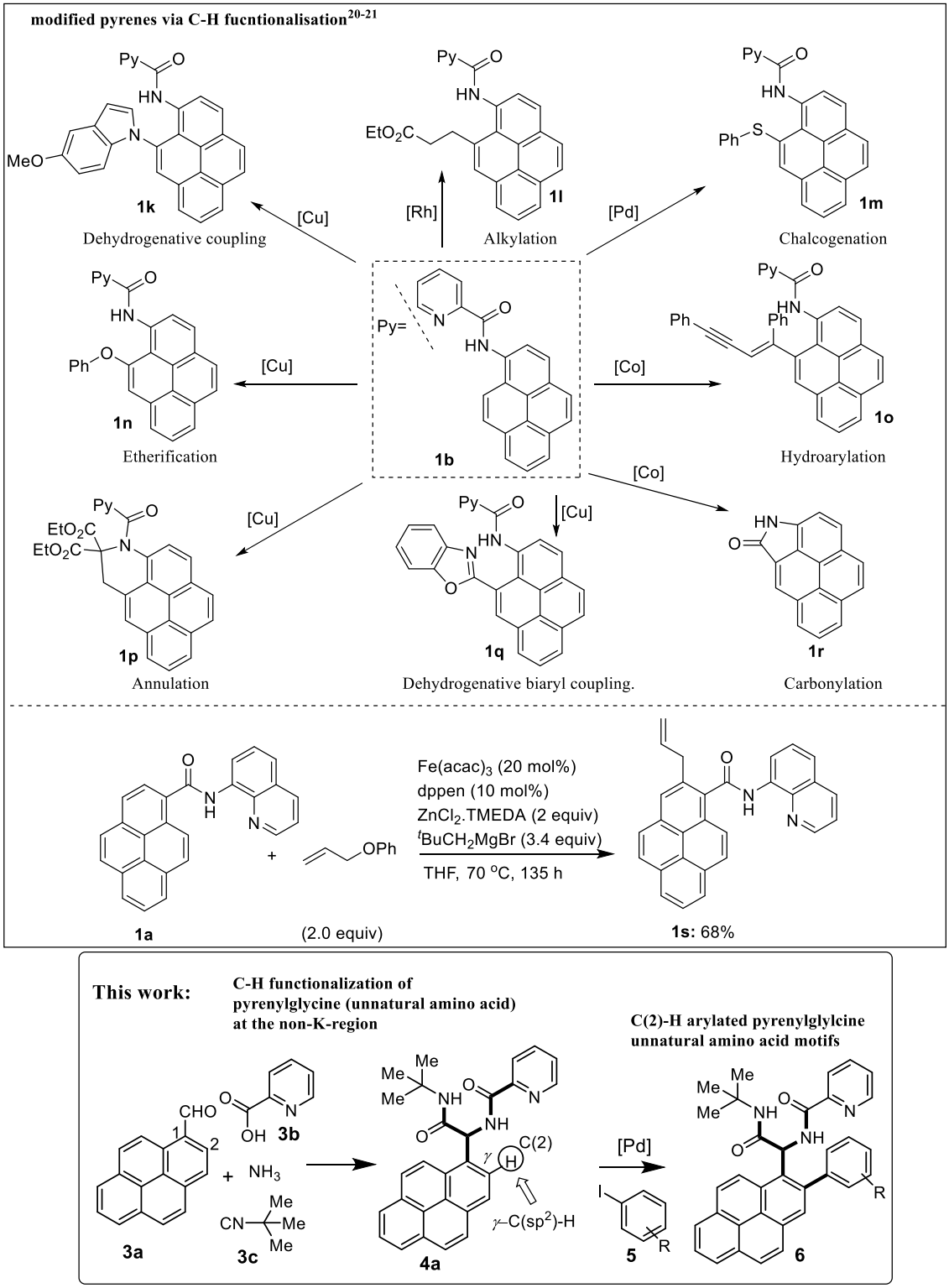
In the last few years, the C–H activation followed by the installation of functional groups at the C-H bonds of small organic molecules has emerged as a reliable synthetic transformation in organic synthesis.[10-12] The modification of various classes of compounds including aromatic, aliphatic, alicyclic, saturated heterocyclic, carbohydrates, and amino acids have been accomplished *via* the C-H functionalization method.[10-12] In particular, the Pd(II)-catalyzed bidentate directing group-aided site-selective C-H functionalization route has been considered a dependable tactic for installing functional groups in the backbone of small organic molecules.[10-18] The picolinamide moiety linked to amine substrates is a well-known bidentate directing group for accomplishing the site-selective γ-C-H functionalization of aromatic and aliphatic amines, respectively.[14-18] Of particular interest, the ortho (or) γ-C(sp^2)−H functionalization of phenylglycine type α-amino acid motifs and ortho (or) δ-C(sp^2)−H functionalization of phenylalanine, tyrosine and β-phenylalanine type α-amino acid motifs have been accomplished using the picolinamide-aided C-H functionalization tactic (Scheme 2).[16-18]

Recently, Polindara-García explored[18a] the Pd(II)-catalyzed C−H bond arylation protocol to access ortho-diaryl, ortho-mono-aryl, and biaryl-diarylmethane-glycinamide derivatives bearing picolinamide as a bidentate directing group and the corresponding substrates were assembled using the Ugi multicomponent reaction.[18] Along this line, we

assembled a new pyrenylglycine substrate possessing the picolinamide moiety *via* the Ugi multicomponent reaction.[19] We then envisioned using the picolinamide directing group-aided C-H functionalization tactic for synthesizing a library of novel pyrenylglycine (pyrene-based glycine) unnatural amino acid derivatives.



Scheme 2. C(2)-Functionalized pyrenylglycine unnatural amino acid scaffolds *via* site-selective C-H functionalization of pyrene at the non-K-region.



Scheme 2. C(2)-Functionalized pyrenylglycine unnatural amino acid scaffolds *via* site-selective C-H functionalization of pyrene at the non-K-region.

Due to the immense utilities of pyrenes, the chemical modification of different sites of pyrenes was attempted by various classic routes.[1,2] In general, the C(2)- and C(7)-positions of pyrene are known as inaccessible sites (viz. non-K-region sites) for functionalization and are considered to be relatively difficult to functionalize *via*

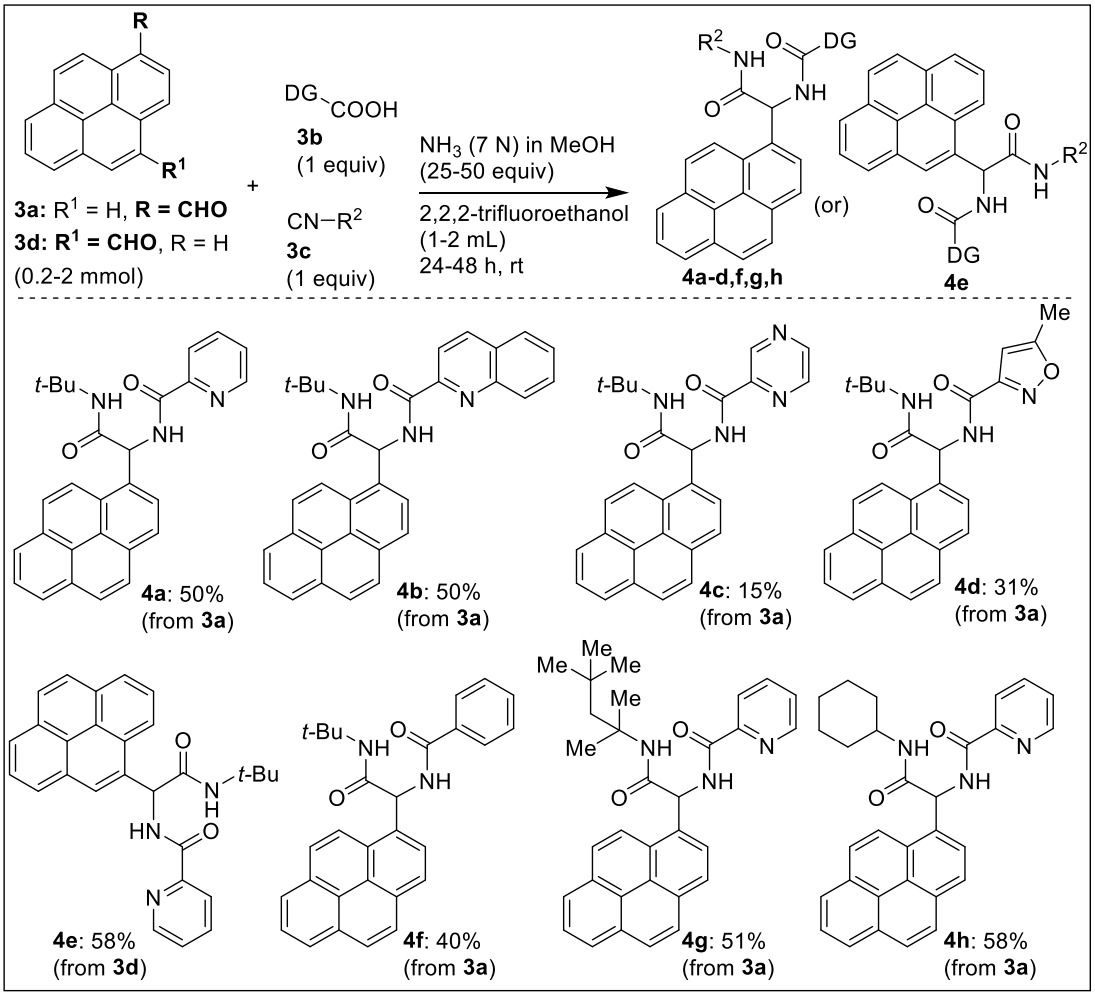
classical routes.[1,2] Nevertheless, the pyrene core has been subjected to the C-H functionalization and ample examples of modified pyrenes have been synthesized *via* the C-H functionalization route (Scheme 2).[20,21] Along this line, recently we reported[20b] the Pd(II)-catalyzed bidentate directing group 8-aminoquinoline-aided *β*-C-H arylation of pyrene-1-carboxylic acid (**1c**) and picolinamide-aided *γ*-C-H arylation of 1-aminopyrene (**1d**) affording C(2) and C(10) arylated pyrene carboxamides (π-extended pyrenes), respectively (Scheme 2).

Taking an impetus from the utility of pyrenes[1,2] and bidentate directing group-aided C-H functionalization route toward modified amino acids,[12,15-18] we aimed to synthesize C(2) arylated pyrenylglycines by using the Pd(II)-catalyzed bidentate directing group-aided ortho and *γ*-C(sp^2)−H arylation strategy. Herein, we report the construction of a library of pyrenylglycine unnatural amino acid motifs with unprecedented examples of C(2)-arylated pyrenylglycines *via* Pd(II)-catalyzed C-H functionalization of C(2)-position present in the non-K-region of pyrene core (Scheme 2).

Results and discussion

At the outset, we carried out the Ugi multicomponent reaction comprising pyrene-1-carboxaldehyde, pyridine-2-carboxylic acid, *tert*-butylisocyanide, and ammonia. This reaction resulted in a new pyrenylglycine unnatural amino acid derivative **4a** (Scheme 3). Under the Ugi reaction the picolinamide bidentate directing group (DG),[18] is automatically incorporated into the pyrenylglycine substrate **4a**. Then, we assembled pyrenylglycinamide substrates **4b,c,d** having the directing groups such as quinoline-2-carboxamide,[22a] pyrazine-2-carboxamide[22b] and 5-methylisoxazole-3-carboxamide.[22c,d] Next, pyrenylglycinamide substrate **4e** was prepared from pyrene-4-carboxaldehyde and pyrenylglycinamide substrate **4f** was assembled using benzoic acid instead of pyridine-2-carboxylic acid. Furthermore, we prepared pyrenylglycinamide substrates **4g,h** using 1,1,3,3-tetramethylbutyl isocyanide and cyclohexyl isocyanide instead of *tert*-butylisocyanide.

Then, we intended to capitalize both the Pd(II)-catalyzed picolinamide DG-aided γ-C(sp^2)-H arylation strategy[16-18] and pyrenylglycine unnatural amino acid substrate **4a** for generating novel examples of C(2)-arylated pyrenylglycines. Table 1 reveals screening reaction conditions for the γ-C(sp^2)-H arylation of **4a** with an aryl iodide **5a**/**5b** using a Pd(II) catalyst and a silver or alkali metal salt additive under the standard reaction conditions used in the bidentate DG-aided C-H arylations.[14-18]

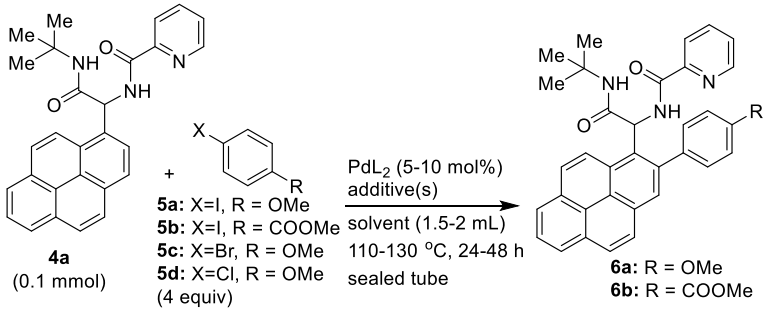


Scheme 3. Assembling of pyrenylglycines **4a-h** possessing DGs *via* Ugi reaction.

The C-H arylation of substrate **4a** with aryl iodide **5a** in the presence of the $Pd(OAc)_2$ catalyst (5-10 mol%), AgOAc or Ag_2CO_3 or KOAc as an additive in *t*-amylOH or *t*-BuOH or toluene at 130 ^oC for 24-48 h gave the corresponding C(2)-arylated pyrenylglycine motifs **6a** in 18-41% yields (entries 1-3, Table 1). The treatment of **4a** with **5a** or **5b** in the presence of the $Pd(OAc)_2$ catalyst (5-10 mol%), KOAc (5 equiv) in toluene at 130 ^oC for 48 h gave the corresponding C(2)-arylated pyrenylglycine motifs **6a** and **6b** in 69% and 46-51% yields (entries 4,12,13, Table 1). To improve the yield of C-H arylation of **4a**, the C-H arylation of **4a** with **5a** was performed using $Pd(OAc)_2$ catalyst (10 mol%), KOAc and in the presence of $CuBr_2$ (0.2 equiv) as an additional additive in *t*-amylOH at 130 ^oC for 24 h, this reaction did not give **6a** (entry 5, Table 1). Then, we tried the C-H arylation of **4a** with **5a**/**5b** in the presence of the $Pd(OAc)_2$ or $Pd(TFA)_2$ catalyst (10 mol%), KOAc and 0.1-0.2 equiv of $CuBr_2$ in toluene at 130 ^oC for 36-48 h. These attempts gave **6a** in 48-74% and **6b** in 53% yields, respectively (entries 6-10,14, Table 1). Notably, the usage of $CuBr_2$ as an additional additive[18a] was

found to give the corresponding C(2)-arylated pyrenylglycine motifs **6a** (74%) and **6b** (69%) in slightly improved yields (entries 9, 15, Table 1).

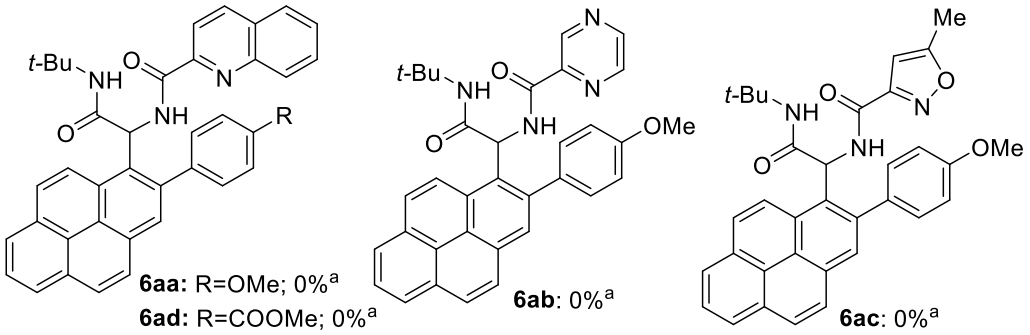
Table 1. Bidentate directing group-assisted Pd(II)-catalyzed, (*ortho*) C(2)-H arylation at the non-K-region of pyrene core.



entry	Catalyst (mol%)	ArI	Additive(s) (equiv)	Conditions	6a/6b yield (%)
1	$Pd(OAc)_2$ (10)	**5a**	AgOAc (2.5)	*t*-amylOH, 24 h,130 °C	**6a:** 18
2	$Pd(OAc)_2$ (5)	**5a**	Ag_2CO_3 (1.5)	*t*-BuOH, 36 h,110 °C	**6a:** 41
3	$Pd(OAc)_2$ (5)	**5a**	KOAc (5)	toluene, 48 h, 130 °C	**6a:** 37
4	$Pd(OAc)_2$ (10)	**5a**	KOAc (5)	toluene, 48 h, 130 °C	**6a:** 69
5	$Pd(OAc)_2$ (10)	**5a**	KOAc (5), $CuBr_2$ (0.2)	*t*-amylOH, 24 h,130 °C	**6a:** 0
6	$Pd(OAc)_2$ (10)	**5a**	KOAc (5), $CuBr_2$ (0.1)	toluene, 36 h, 130 °C	**6a:** 57
7	$Pd(OAc)_2$ (10)	**5a**	KOAc (5), $CuBr_2$ (0.2)	toluene, 36 h, 130 °C	**6a:** 55
8	$Pd(TFA)_2$ (10)	**5a**	KOAc (5), $CuBr_2$ (0.2)	toluene, 36 h, 130 °C	**6a:** 48
9	**$Pd(OAc)_2$ (10)**	**5a**	**KOAc (5), $CuBr_2$ (0.1)**	**toluene, 48 h, 130 °C**	**6a: 74**
10	$Pd(OAc)_2$ (10)	**5a**	KOAc (5), $CuBr_2$ (0.2)	toluene, 48 h, 130 °C	**6a:** 52
11	$Pd(OAc)_2$ (10)	**5a**	KOAc (5), $CuBr_2$ (0.2)	neat, 48 h, 130 °C	**6a:** 76
12	$Pd(OAc)_2$ (5)	**5b**	KOAc (2)	toluene, 48 h, 130 °C	**6b:** 46
13	$Pd(OAc)_2$ (10)	**5b**	KOAc (5)	toluene, 48 h, 130 °C	**6b:** 51
14	$Pd(OAc)_2$ (5)	**5b**	KOAc (5), $CuBr_2$ (0.1)	toluene, 48 h, 130 °C	**6b:** 53
15	$Pd(OAc)_2$ (10)	**5b**	KOAc (5), $CuBr_2$ (0.1)	toluene, 48 h, 130 °C	**6b:** 69
16	$Pd(OAc)_2$ (10)	**5b**	KOAc (5), $CuBr_2$ (0.1)	neat, 48 h, 130 °C	**6b:** 59

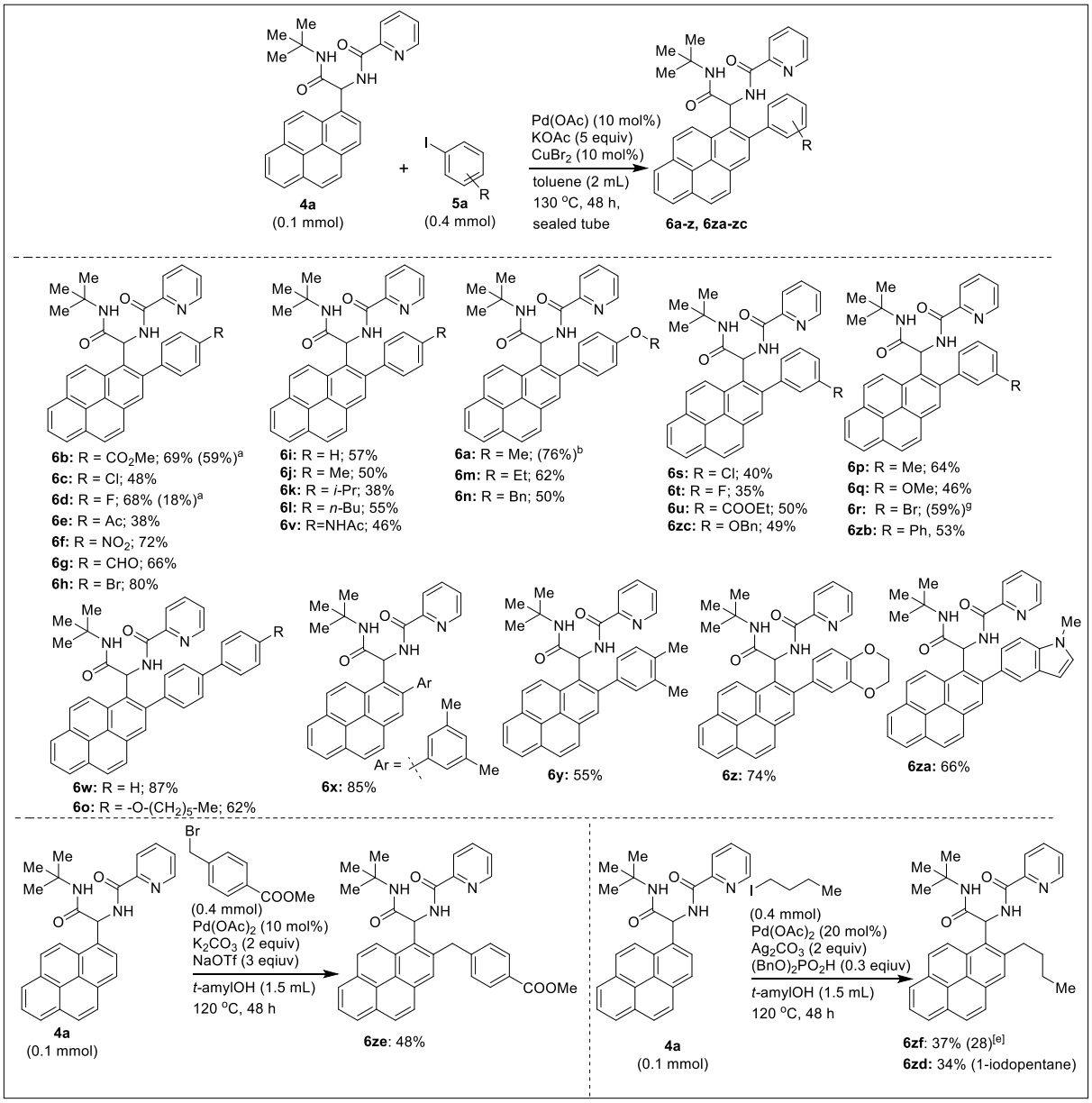
17[a,b]	$Pd(OAc)_2$ (10)	**5a**	KOAc (5), $CuBr_2$ (0.1)	toluene, 48 h, 130 °C	**6a:** 78
18[a,c]	$Pd(OAc)_2$ (10)	**5a**	KOAc (5), $CuBr_2$ (0.1)	toluene, 48 h, 130 °C	**6a**: 70
19[a,d]	$Pd(OAc)_2$ (10)	**5a**	KOAc (5), $CuBr_2$ (0.1)	toluene, 48 h, 130 °C	**6a**: 63
20[a,e]	$Pd(OAc)_2$ (10)	**5a**	KOAc (5), $CuBr_2$ (0.1)	toluene, 48 h, 130 °C	**6a**: 32
21[a]	$Pd(OAc)_2$ (10)	**5c**	KOAc (5), $CuBr_2$ (0.1)	toluene, 48 h, 130 °C	**6a**: traces
22[a]	$Pd(OAc)_2$ (10)	**5d**	KOAc (5), $CuBr_2$ (0.1)	toluene, 48 h, 130 °C	**6a**: traces

[a] **4a** (0.05 mmol), $CuBr_2$ (0.1 equiv), toluene (1.5 mL), sealed tube.
[b] **5a** (4 equiv), recovery of **5a** = 25 mg. [c] **5a** (3 equiv), recovery of **5a** = 15 mg.
[d] **5a** (2 equiv), recovery of **5a** = <5 mg. [e] **5a** (1 equiv), recovery of **5a** = Not detected.



The treatment of **4a** with **5a** or **5b** in the presence of $Pd(OAc)_2$, KOAc, and $CuBr_2$ in neat condition also gave the corresponding products **6a** and **6b** in 76% and 59% yields (entries 11,16, Table 1). The Pd(II)-catalyzed C(2)-H arylation of pyrenylglycine substrates **4b,c,d** possessing the other DGs (e.g., quinoline-2-carboxamide, pyrazine-2-carboxamide and 5-methylisoxazole-3-carboxamide) did not yield the corresponding products **6aa-6ad** (Table 1). While these directing groups have been used for obtaining the *ortho* C-H arylations in low to moderate yields in other aromatic amine substrates.[16a,17b,22a-d] In the current work involving pyrene-based glycine substrates **4b,c,d**, these DGs were not effective and the reason why these DGs are not effective is not clear at this stage. While the C-H arylation of **4a** in the absence of $CuBr_2$ is also affording the product **6a**/**6b** (entries 1-4, 12,13, Table 1). The role of $CuBr_2$ seems to be merely acting as an additive or oxidant in promoting the reaction to afford improved yield of **6a**/**6b** and $CuBr_2$ seems to be playing no role as an active catalytic species in the activation process through the picolinamide coordination.[18a]

Additionally, we tested the C-H arylation of **4a** using different equivalents of **5a**. The reaction using 3-4 equiv of **5a** gave **6a** in 70-78% yield and in these reactions, a demonstrable amount of recovery of **5a** was noted (entries 17,18, Table 1). The reaction using 1-2 equiv of **5a** gave **6a** in 32-63% yield and in these reactions, a low to considerable amount of recovery of **5a** was noted (entries 19,20, Table 1). Finally, we also tested the C-H arylation of **4a** using an aryl bromide **5c** or an aryl chloride **5d**. These trials were not fruitful and **6a** was not obtained in demonstrable amounts (entries 21,22, Table 1).

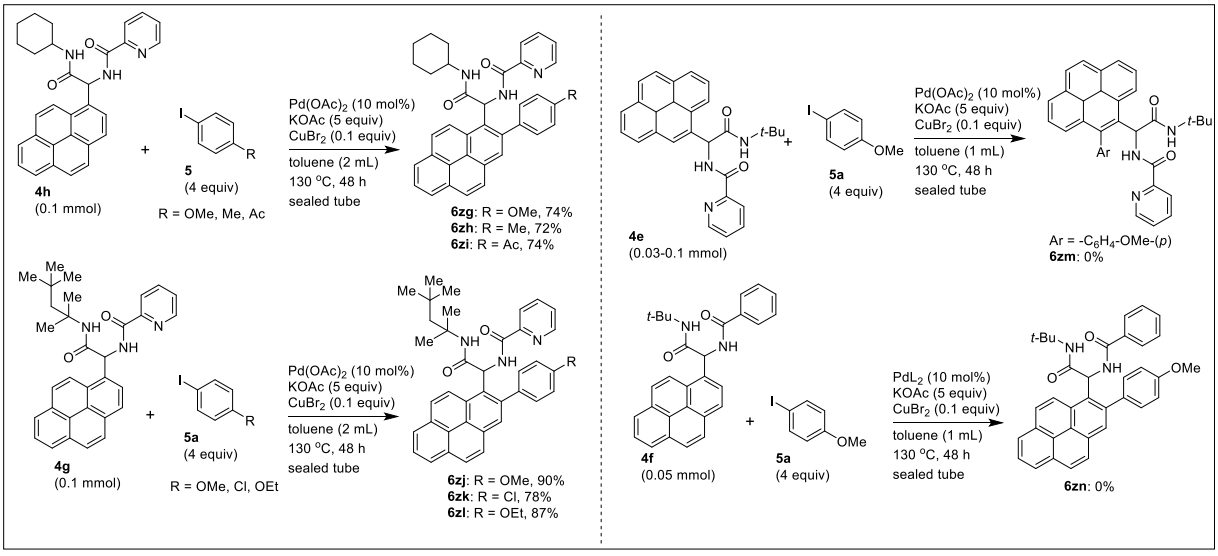


[a]ArI (0.5 mmol) and neat condition in sealed tube (purged with N_2 atm). [b]$CuBr_2$ (20 mol%) and neat condition. [e]4a (0.1 mmol), 1-iodobutane (0.4 mmol), $Pd(OAc)_2$ (10 mol%), KOAc (5 equiv), 1,4-dioxane (1.5 mL), 130 °C, 72 h. [g]ArI (0.5 mmol), sealed tube (purged with N_2 atm).

Scheme 4. Construction of pyrenylglycine unnatural amino acid motifs from **4a.**

Next, we wished to expand the substrate scope and construct a library of C(2)-arylated pyrenylglycines. Substrate **4a** was treated with aryl iodides possessing a substituent at the *para* or *meta* position or PhI in the presence of the $Pd(OAc)_2$ catalyst (10 mol%), KOAc (5 equiv) and $CuBr_2$ (0.1 equiv) in toluene at 130 °C for 48 h. These attempts yielded the corresponding C(2)-arylated pyrenylglycine motifs **6a-n**, **6p-v**, and **6zc** in 35-80% yields (Scheme 4). The Pd(II)-catalyzed γ-C-H arylation of **4a** with iodobiphenyls or disubstituted aryl iodides gave the corresponding C(2)-arylated pyrenylglycine motifs **6o,w,x,y, 6zb** in 53-87% yields (Scheme 4).

We then performed the Pd(II)-catalyzed γ-C-H arylation of **4a** with 6-iodo-1,4-benzodioxane or heteroaryl iodide such as 5-iodo-*N*-methylindole. These reactions gave the corresponding C(2)-arylated pyrenylglycine motifs **6z** and **6za** in 66-74% yields (Scheme 4). The products **6a** and **6b** were also obtained in neat conditions with satisfactory yields. Attempts comprising the arylation of **4a** with other aryl iodides in neat conditions were sluggish and for example, product **6d** obtained 18 and 68% yields when performed in neat and toluene solvent conditions, respectively. The γ-C-H benzylation and alkylation of **4a** gave the corresponding C(2)-benzylated pyrenylglycine **6ze** in 48% yield and C(2)-alkylated pyrenylglycines **6zf, 6zd** in 28-37% yields.



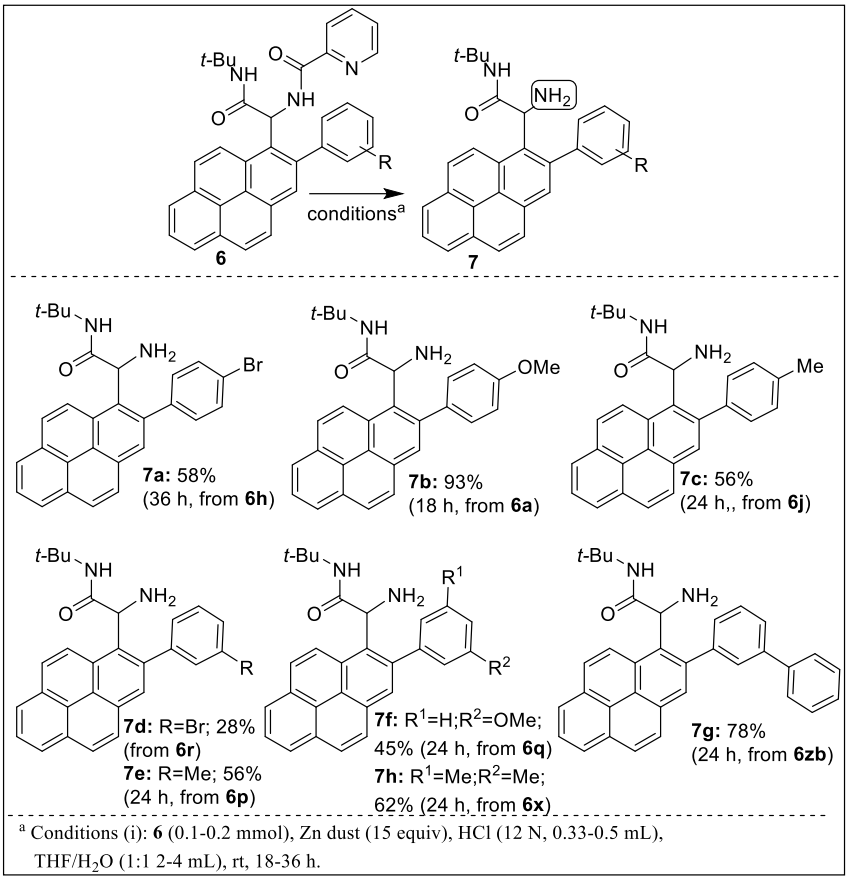
Scheme 5. Construction of pyrenylglycine unnatural amino acid motifs from **4e-h.**

Having performed the Pd(II)-catalyzed γ-C-H arylation of pyrene-based glycine substrate **4a** which was prepared using *tert*-butylisocyanide, we then wished to attempt the C-H arylation of pyrene-based glycine substrates **4g,h** which were prepared using 1,1,3,3-tetramethylbutyl isocyanide and cyclohexyl isocyanide, respectively.

Accordingly, substrates **4g,h** were treated with various *para*-substituted aryl iodides in the presence of the $Pd(OAc)_2$ catalyst (10 mol%), KOAc (5 equiv) and $CuBr_2$ (0.1 equiv) in toluene at 130 ^oC for 48 h. These reactions successfully afforded the corresponding C(2)-arylated pyrenylglycine unnatural amino acid motifs **6zg, 6zh, 6zi, 6zj, 6zk** and **6zl** in 72-90% yields (Scheme 5). The C(2)-arylated pyrenylglycine unnatural amino acid motifs **6a-z,** and **6za-zl** were obtained from the parent substrate pyrene-1-carboxaldehyde **3a**. Accordingly, the γ-C-H arylation successfully occurred at the C2 position of the corresponding pyrenylglycine substrates **4a**, **4g** and **4h**.

Subsequently, we wished to attempt the Pd(II)-catalyzed γ-C-H arylation of pyrene-based glycine substrate **4e** which was prepared using pyrene-4-carboxaldehyde **3d**. Accordingly, substrate **4e** was treated with an aryl iodide **5a** in the presence of the $Pd(OAc)_2$ catalyst (10 mol%), KOAc (5 equiv), and $CuBr_2$ (0.1 equiv) in toluene at 130 ^oC for 48 h. Unfortunately, substrate **4e** did not give the expected γ-C-H arylated product (C(5)-arylated pyrenylglycine) **6zm** (Scheme 5). This may be due to the nature of the specific substrate **4e** and the inherent steric hindrance present in substrate **4e** (viz. the γ-C-H and C(5)-H bond has the fusion of the next aryl ring at the C(6) position, which may hinder the C(5)-H arylation in **4e**). It is a generally observed trend in the literature reports that the *ortho* C-H arylation of the *meta*-substituted substrate is sluggish or ineffective due to steric hindrance.[11-18] Finally, pyrenylglycinamide substrate **4f** which was assembled using benzoic acid instead of pyridine-2-carboxylic acid was subjected to the Pd(II)-catalyzed γ-C-H arylation conditions which were used for substrate **4a**. Notably, the substrate **4f** did not give the expected γ-C-H arylated product **6zn** (Scheme 5).

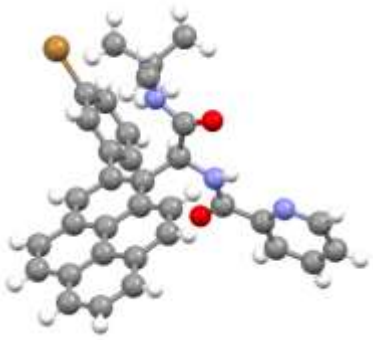
To reveal the synthetic utility of the pyrenylglycines, the C(2)-arylated pyrenylglycines **6a,h,j,p,q,r,x,** and **6zb** were subjected to the Zn/HCl-mediated picolinoyl moiety removal. These reactions gave the corresponding picolinamide DG-free C(2)- arylated pyrenylglycine unnatural amino acid motifs **7a-h** possessing free NH_2 group in 28-93% yields (Scheme 6).



Scheme 6. Synthesis of pyrenylglycines **7.**

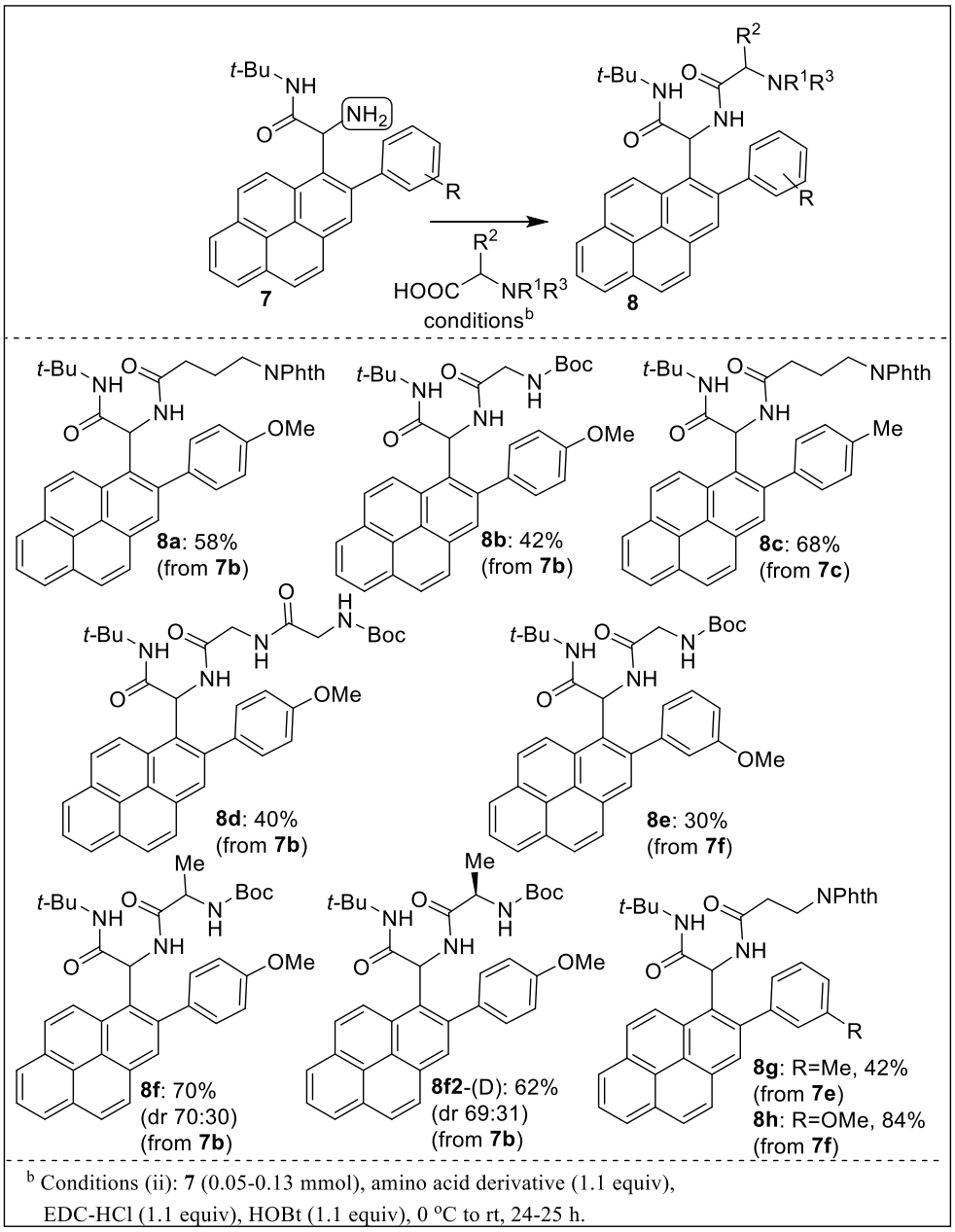
Subsequently, the C(2)-arylated pyrenylglycine **7b,c** possessing a free NH_2 group was subjected to the peptide coupling reaction with *N*-phthaloyl-GABA to afford the pyrenylglycine-GABA peptide **8a,c** in 58-68% yields (Scheme 7). Next, **7b,f** were subjected to the coupling with *N*-Boc-Gly to afford the pyrenylglycine-glycine peptide **8b,e** in 30-42% yields. A pyrenylglycine-glycine-glycine tripeptide **8d** was obtained from the coupling of **7b** and *N*-Boc-Gly-Gly. Next, **7b** was subjected to the coupling with (DL)-*N*-Boc-Ala or (D)-*N*-Boc-Ala to afford corresponding pyrenylglycine-Ala **8f** and **8f2**-(D). Furthermore, *N*-Phthaloyl-*β*-alanine was coupled with **7e,f** to afford the pyrenylglycine-*β*-alanine peptides **8g,h**.

We ascertained the photophysical properties including UV-Vis absorption spectra of all the pyrenylglycines) and the preliminary fluorescence emission spectra of representative pyrenylglycine motifs synthesized in this work (Figure 1). We also performed the fluorescence quantum yield (Φ) calculation of representative compounds; **6a** (Φ =



0.139), **6j** (Φ = 0.069), **6y** (Φ = 0.226), **6z** (Φ = 0.169), **7h** (Φ = 0.089), **8a** (Φ = 0.004), the integrated fluorescence intensity vs absorbance plots for these compounds are given figure2, table 2.

Figure 2. X-ray structure (ball and stick model, the unit cell contains two molecules) of compound **6r.**



Scheme 7. Synthesis of pyrenylglycine peptides **8.**

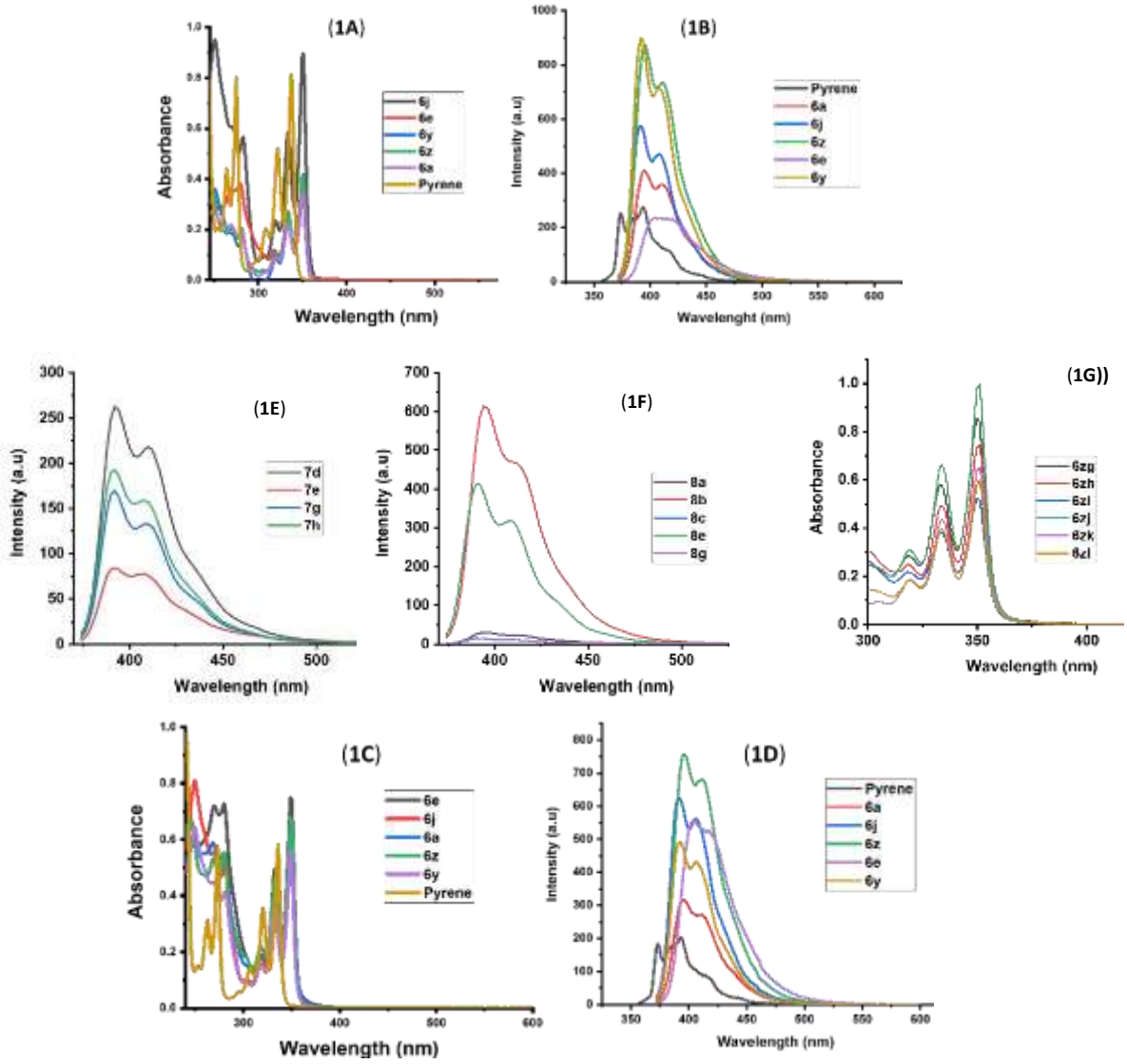
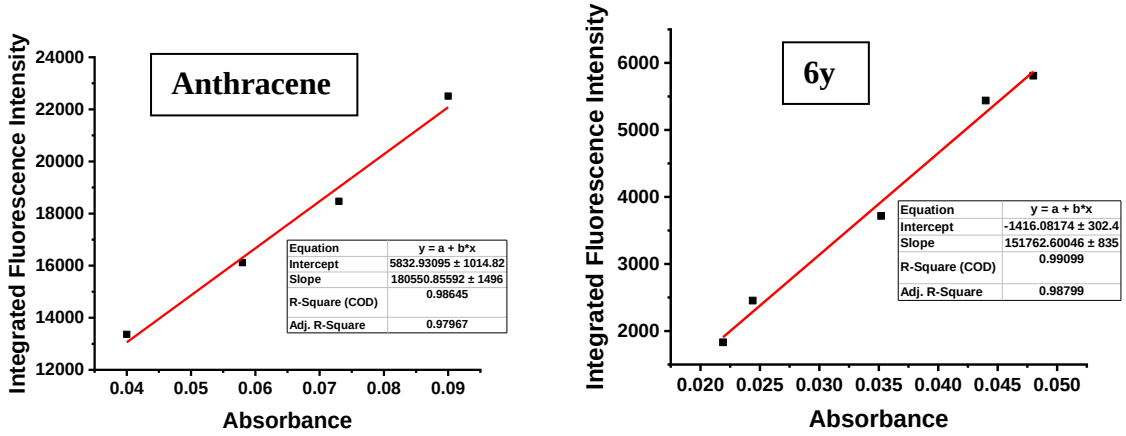


Figure 1. Optical absorption and emission spectra of representative compounds.

(**1A**): The absorption spectra of **6a, 6j, 6z, 6e** and **6y** (c = 0.02 g/100 mL in $CHCl_3$) in $CHCl_3$, $\lambda_{max\ (absorption)}$ (nm) = Pyrene: 337, **6a**: 349, **6j**: 349, **6z**: 349, **6e**: 349, **6y**: 350. (**1B**): Emission spectra of **6a, 6j, 6z, 6e** and **6y** in $CHCl_3$ (c = 3.8 µM) at the excitation wavelength of 350 nm $\lambda_{max\ (emission)}$ (nm) = Pyrene: 393, **6a**: 395, **6j**: 390, **6z**: 396, **6e**: 404, **6y**: 392. (**1C**): The absorption spectra of **6a, 6j, 6z, 6e** and **6y** (c = 0.02 g/100 mL in THF) in THF, $\lambda_{max\ (absorption)}$ (nm) = Pyrene: 336, **6a**: 349, **6j**: 349, **6z**: 350, **6e**: 349, **6y**: 349. (**1D**): Emission spectra of **6a, 6j, 6z, 6e** and **6y** in THF (c = 3.8 µM) at the excitation wavelength of 350 nm $\lambda_{max\ (emission)}$ (nm) = Pyrene: 392, **6a**: 395, **6j**: 391, **6z**: 396, **6e**: 405, **6y**: 392. (**1E**) and (**1F**): Emission spectra of **7d, 7e, 7g, 7h, 8a, 8b, 8c, 8e** and **8g** (c = 6.06 µM) in $CHCl_3$ at the excitation wavelength of 350 nm $\lambda_{max\ (emission)}$ (nm) = **7d**: 392, **7e**: 392, **7g**: 392, **7h**: 392, **8a**: 396, **8b**: 396, **8c**: 390, **8e**: 390, **8g**: 390. (**1G**): The absorption spectra of **6zg, 6zh, 6zi, 6zj, 6zk** and **6zl** (c = 0.01 g/100 mL in $CHCl_3$) in $CHCl_3$ $\lambda_{max\ (absorption)}$ (nm) = **6zg, 6zh, 6zi, 6zj, 6zk** and **6zl =** 350 nm.



The quantum yield was calculated following the given equation. $\Phi_X = \Phi_{ST}\ (m_X / m_{ST})\ (\eta^2_X / \eta^2_{ST})$, using anthracene as standard ($\Phi_{ST} = 0.27$), where Φ is the quantum yield, η is the refractive index of solvent (ethanol, $\eta = 1.36$), m is slope, X is the sample and ST the standard.

Figure 2. Integrated fluorescence intentisity vs Absorbance plot of compound anthracene and 6y.

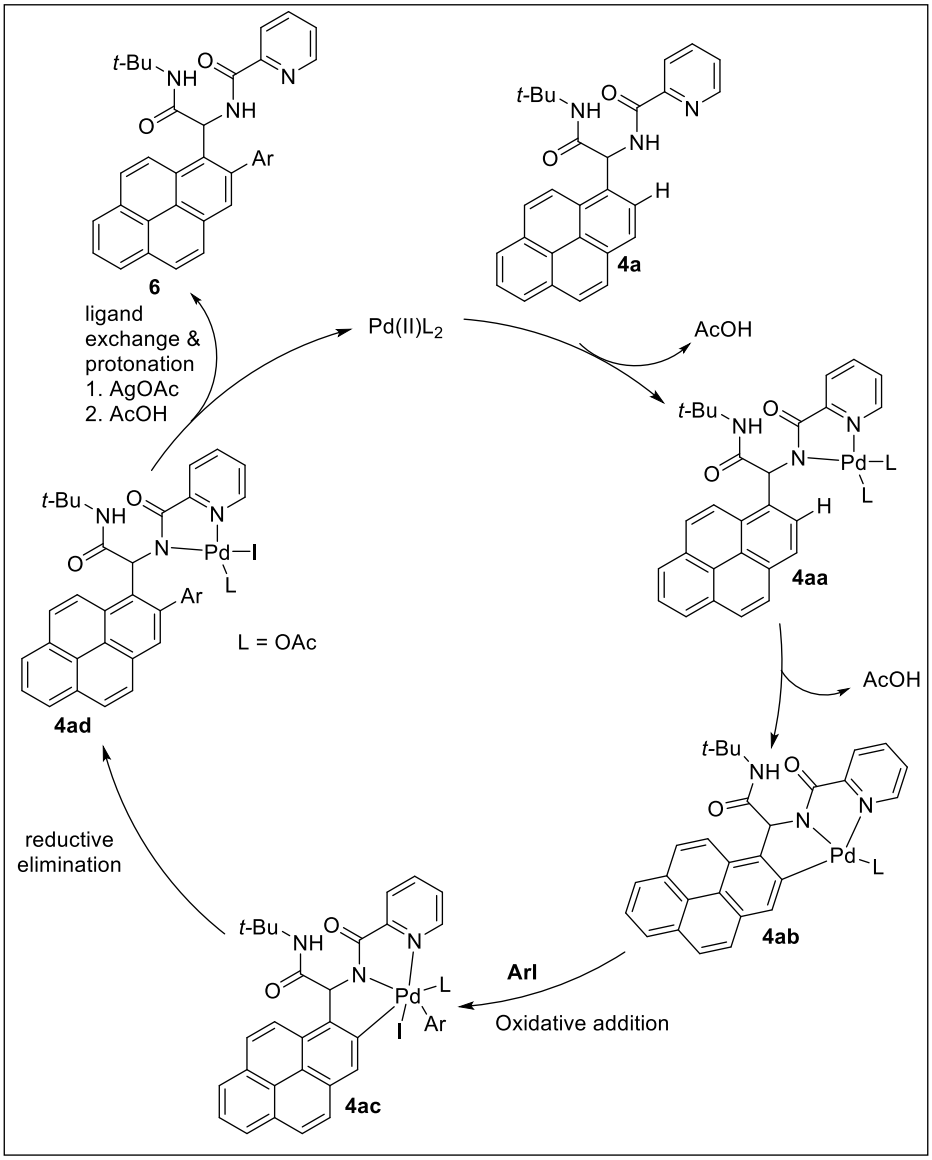
Table2. Quantum yield of **6y**, **6a**, **6j**, **6z**, **7h**, **8a**.

Compound	Slope (m_X)	Quantum yield (Φ)
6y	151762.60046	0.226
6a	93113.22571	0.139
6j	46274.97295	0.069
6z	112328.07115	0.169
7h	60141.06904	0.089
8a	2969.97295	0.004

The synthesized pyrenylglycines are characterized by NMR and HRMS analysis data. Additionally, the X-ray structure of representative compound **6r** (Figure 2) was obtained, which corroborated the structure of pyrenylglycine and the regioselectivity of C(2)-arylation of pyrene **4a**. In concurrence with literature reports, the bidentate directing group picolinamide-assisted γ-C(sp^2)-H arylation of pyrenylglycine **4a** discussed in this paper is believed to undergo *via* the well-documented Pd^{II}-Pd^{IV} catalytic cycle.[11-18] It may be noted that the control experiment comprising of Pd(II)-catalyzed γ-C-H arylation of pyrenylglycinamide substrate **4f**, which has a simple benzamide moiety as the directing group did not undergo the C-H arylation. This revealed the necessity and role of the picolinamide directing group in substrate **4a** which gave the γ-C-H arylated products **6a-z** and **6za-zl**.

In concurrence with the literature reports,[11-18] the bidentate directing group picolinamide helps in promoting the γ-C(sp^2)-H arylation of **4a** and it provides the chelation assistance and directs the Pd(II)-catalyzed C-H arylation process in the well documented catalytic cycle.[11,18a] Accordingly, a plausible reaction pathway for the bidentate directing group picolinamide-

assisted Pd(II)-catalyzed arylation of the γ-C(sp^2)-H bond of pyrene substrate **4a** is proposed based on the literature reports (Scheme 8).[11-18] Coordination of the picolinamide directing group in pyrene-based glycine substrate **4a** to the Pd(II) metal center is followed by concerted metalation deprotonation (CMD), generates the plausible five-membered Pd(II) intermediate species **4ab**. Oxidative addition of the Pd(II) intermediate species **4ab** with an aryl iodide forms the Pd(IV) species **4ac**. Subsequently, the Pd(IV) intermediate species **4ac** undergoes reductive elimination to generate the new C–C bond in pyrene-based glycine unnatural amino acid derivative **4ad**. Then, halide ion abstraction by a halide ion scavenger (e.g., AgOAc) followed by the protonolysis of the Pd(II) intermediate species **4ad** generates the corresponding γ-C(sp^2)-H arylated product **6** and the Pd(II) catalyst is regenerated in the catalytic cycle (Scheme 8).[11-18] Further support for the proposed mechanism can be drawn from a recent report by Polindara-García, which delineated a plausible mechanism for ortho C-H arylation of arylglycine-type substrates.[18a]



Scheme 8. Plausible mechanism in concurrence with the literature reports.[11-18] Pd(II)-catalyzed picolinamide DG-aided γ-C-H arylation of C2 position of pyrene-based glycine substrate **4a.**

Conclusions

In summary, we have shown the preliminary results of our investigations on synthesizing novel pyrenylglycine unnatural amino acid derivatives *via* C-H functionalization of pyrene at the non-K-region. We assembled a new pyrenylglycine possessing the picolinamide moiety *via* the Ugi multicomponent reaction. The picolinamide moiety installed in pyrene is a well-known bidentate directing group for accomplishing the site-selective γ-C-H functionalization. Consequently, pyrenylglycine possessing the picolinamide moiety was subjected to the Pd(II)-catalyzed C(2)-H arylation at the non-K-region to afford a library of unprecedented examples of C(2)-H arylated pyrenylglycines. Additionally, pyrenylglycine-based small peptides were assembled using C(2)-arylated pyrenylglycines The X-ray structure of a representative

compound was obtained, which corroborated the structure of pyrenylglycine and the regioselectivity of C(2)-H arylation of the pyrene at the non-K-region. Transformations involving pyrenylglycines and synthetic methods toward pyrenylglycine motifs are rarely explored. Accordingly, this work is an unprecedented contribution towards enriching the library of pyrenes and pyrenylglycine unnatural amino acid motifs. Further investigations comprising the synthesis of chiral pyrenylglycine and finding applications and photophysical properties of these compounds will be attempted and reported in the near future.

Experimental

General. ^{1}H and $^{13}C\{1H\}$ NMR spectra of compounds were recorded (using TMS as an internal standard) in 400 and ~101 MHz spectrometers, respectively. The HRMS analysis data of samples were obtained from the QTOF mass analyzer using the electrospray ionization (ESI) method. FT-IR spectra of samples were recorded as neat or thin films. Column chromatography purification of crude reaction mixtures was carried out on silica gel (100−200 mesh). Reactions were conducted in anhydrous solvents under a nitrogen atmosphere wherever required. Organic layers obtained after the workup were dried using anhydrous Na_2SO_4. Thin layer chromatography (TLC) analyses were performed on silica gel or alumina plates and components were visualized by UV light or under iodine vapor. Isolated yields of all the products are reported and yields were not optimized. The UV-Vis absorption spectra of compounds recorded (concentration (c) = 0.02 g/100 mL in $CHCl_3$ or concentration (c) = 0.01 g/100 mL in $CHCl_3$) in $CHCl_3$.[23]

General procedure for the synthesis of compounds 4a-h: A solution of aromatic aldehyde (1 equiv), carboxylic acid (1 equiv), ammonia solution (7 N in methanol, 25-50 equiv), and isocyanide (1 equiv) in TFE (2 mL) was stirred at room temperature for 24 h. The reaction mixture was diluted with CH_2Cl_2 and washed with water and brine. The organic extracts were combined, and dried over anhydrous Na_2SO_4 and the solvent was evaporated. The crude mixture was subjected to column chromatography to afford the compound **4a-h** (Procedure adapted from ref. L. A. Polindara-García et al *Eur. J. Org. Chem.*, 2022, e202101517).

General procedure for the synthesis of compounds 6a-z, 6za-6zc, 6zg-6zn: A solution of pyrenylglycinamide **4a** (1 equiv), aryl iodide (4 equiv), KOAc (5 equiv), $Pd(OAc)_2$ (10 mol%),

and $CuBr_2$ (10 mol%) in dry toluene (1.5 mL) was heated in a sealed tube vial under conventional heating (oil bath) at 130 ºC for 48 h. The tube was flashed with nitrogen before heating. The reaction mixture was concentrated under reduced pressure. The crude mixture was subjected to column chromatography to afford the corresponding C-H arylated pyrenylglycine.

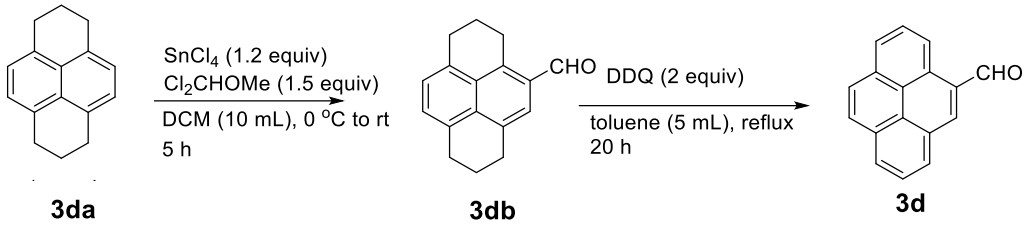
General procedure for the synthesis of compounds 6ze: A solution of pyreneglycinamide **4a** (1 equiv), methyl 4-(bromomethyl)benzoate (4 equiv), $Pd(OAc)_2$ (10 mol%), K_2CO_3 (2 equiv), NaOTf (3 equiv) in *tert*-amylOH (1.5 mL) was heated in a sealed tube vial under conventional heating (oil bath) at 120 ºC for 48 h. The tube was flashed with nitrogen before heating. The reaction mixture was concentrated under reduced pressure. The crude mixture was subjected to column chromatography to afford the compound **6ze**.

General procedure for the synthesis of compounds 6zf: A solution of pyreneglycinamide **4a** (1 equiv), 1-iodobutane (4 equiv), $Pd(OAc)_2$ (10 mol%), Ag_2CO_3 (2 equiv), $(BnO)_2PO_2H$ (0.3 equiv) in *tert*-amylOH (1.5 mL) was heated in a sealed tube vial under conventional heating (oil bath) at 120 ºC for 48 h. The tube was flashed with nitrogen before heating. The reaction mixture was concentrated under reduced pressure. The crude mixture was subjected to column chromatography to afford the compounds **6zf**.

General procedure for the synthesis of compounds 6zd: A solution of pyreneglycinamide **4a** (1 equiv), 1-iodopentane (4.0 equiv), $Pd(OAc)_2$ (10 mol%), KOAc (2.0 equiv) in dry 1,4-dioxane (1.5 mL) was heated in a sealed tube vial under conventional heating (oil bath) at 130 ºC for 48 h. The tube was flashed with nitrogen before heating. The reaction mixture was concentrated under reduced pressure. The crude mixture was subjected to column chromatography to afford the compound **6zd**.

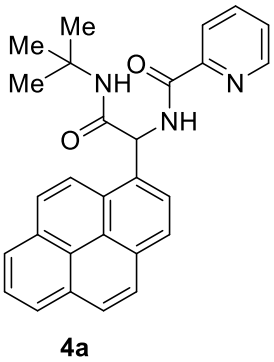
General procedure for the synthesis of compounds 7a-h: To an appropriate arylated compound **6** (1 equiv) dissolved in H_2O/THF (1:1, 2-4 mL), 12 N HCl (0.33-0.5 mL) was added. The mixture was stirred at rt for 15 min. Zinc dust (15 equiv) was then added in three portions and the mixture was stirred at rt for 18-36 h. The mixture was transferred to a separating funnel with 2 N NaOH (20 mL) and extracted with ethyl acetate. The reaction mixture was concentrated under reduced pressure. The crude mixture was subjected to column chromatography to afford the compound **7a-h** (the plicolinamide directing group removal procedure was carried out using the reported procedure)[16a,17b,22e]

General procedure for the synthesis of compounds 8a-h and 8f2-(D): An appropriate amount of *N*-protected amino acid (1 equiv), *N*-(3-dimethylaminopropyl)-*N*′-ethylcarbodiimide hydrochloride (1.1 equiv), 1-hydroxybenzotriazole hydrate (1.1 equiv) in dry DCM (5 mL) was stirred for 1 h at 0 °C under a nitrogen atmosphere. Then, an appropriate amount of amine compound **7** (1 equiv) was added to the above mixture and stirred for 24-25 h at room temperature. The resulting solution was then subjected to aqueous workup and washed with aqueous $NaHCO_3$ solution (two times). The resulting solution mixture was concentrated and purified on silica gel column chromatography (EtOAc/hexane) to give the corresponding pyrene-based peptides.



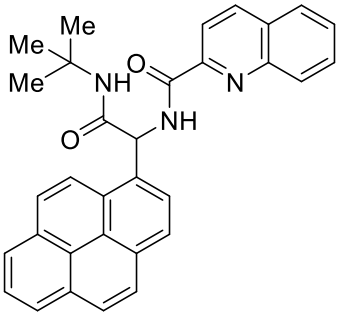
General procedure for the synthesis of pyrene-4-carbaldehyde (3d): To a solution of 1,2,3,6,7,8-hexahydropyrene (**3da**, 208 mg, 1 mmol) in CH_2Cl_2 (10 mL) was added stannic chloride (140 µL, 1.2mmol), and the mixture was cooled to 0°C under a nitrogen atmosphere. Then, 1,1′-dichlorodimethyl ether (136 µL, 1.5 mmol) was added by a syringe, and the mixture was stirred at 0°C for 5 h. The reaction was monitored by TLC. After completion, the reaction mixture was gradually warmed to rt and then quenched with ice-water, acidified by dilute hydrochloric acid, and extracted with DCM. The organic phase was dried over anhydrous Na_2SO_4, filtrated, and then concentrated to get the crude product **3db** which is used for next step without purification. To a solution of 1,2,3,6,7,8-hexahydropyrene-4-carbaldehyde (**3db**, 1 mmol) in dry toluene (5 mL) was added DDQ (2 equiv) and the reaction mixture was heated at 100 °C for 20 h. The reaction was monitored by TLC. The reaction mixture was concentrated under reduced pressure. The crude mixture was subjected to column chromatography to afford the compound **3d** (86% yield). (The preparation of **3d** was carried out using reported procedure: (a) Li, P.-F.; Chen, C.-F. *J. Org. Chem*. **2012**, *77*, 9250. (b) Bair, K. W.; Andrews, C. W.; Tuttle, R. L.; Knick, V. C.; Cory, M.; McKee, D. D. *J. Med. Chem.* **1991**, *34*, 1983).

***N*-(2-(*Tert*-butylamino)-2-oxo-1-(pyren-1-yl)ethyl)picolinamide (4a):** The compound **4a** was obtained after purification by column chromatography on silica gel (EtOAc:hexane = 30:70) as a yellow-coloured solid (435 mg, 50%, 2 mmol scale); R_f (50% EtOAc/hexane) 0.25; mp: 210-212 ^oC; IR (DCM): 3335, 2976, 1665, 1510, 755 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ_H 9.45 (1H, d, J = 7.1 Hz), 8.58-8.55 (2H, m), 8.23-8.21 (5H, m), 8.14-8.03 (4H, m), 7.82-7.77 (1H, m), 7.41-7.37 (1H, m), 6.51 (1H, d, J = 7.2 Hz), 5.48 (1H, s), 1.29 (9H, s); $^{13}C\{^1H\}$ NMR (~101 MHz, $CDCl_3$): δ_C 169.5, 164.1, 149.5, 148.3, 137.1, 131.6, 131.5, 131.2, 130.7, 129.0, 128.7, 127.9, 127.3, 126.6, 126.2, 126.2, 125.6, 125.5, 125.3, 125.3, 124.7, 122.6, 122.2, 55.4, 52.0, 28.5; HRMS (ESI): *m/z* $[M+H]^+$ calcd for $C_{28}H_{26}N_3O_2$: 436.2025 found, 436.2012.



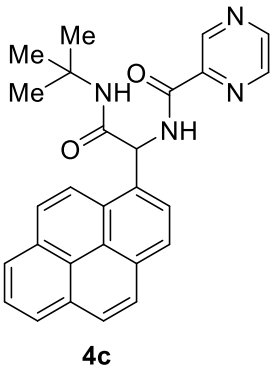
4a

***N*-(2-(*Tert*-butylamino)-2-oxo-1-(pyren-1-yl)ethyl)quinoline-2-carboxamide (4b):** The compound **4b** was obtained after purification by column chromatography on silica gel (EtOAc:hexane = 30:70) as a brown-coloured solid (121 mg, 50%, 0.5 mmol scale); R_f (50% EtOAc/hexane) 0.25; mp: 240-242 ^oC; IR (DCM): 3321, 2973, 1664, 1502, 755 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ_H 9.68 (1H, d, J = 7.4 Hz), 8.68 (1H, d, J = 9.3 Hz), 8.34 (1H, d, J = 8.0 Hz), 8.23-8.10 (7H, m), 8.03 (2H, s), 7.96 (1H, t, J = 7.6 Hz), 7.73-7.65 (2H, m), 7.53-7.49 (1H, m), 6.74 (1H, d, J = 7.4 Hz), 5.98 (1H, s), 1.34 (9H, s); $^{13}C\{^1H\}$ NMR (~101 MHz, $CDCl_3$): δ_C 169.6, 164.2, 149.1, 146.4, 137.1, 131.6, 131.4, 131.0, 130.5, 129.9, 129.8, 129.1, 129.0, 128.7, 127.8, 127.8, 127.4, 127.2, 126.3, 126.0, 125.5, 125.3, 125.2, 124.6, 122.6, 118.5, 55.3, 51.9, 28.5; HRMS (ESI): *m/z* $[M+H]^+$ calcd for $C_{32}H_{28}N_3O_2$: 486.2182 found, 486.2181.



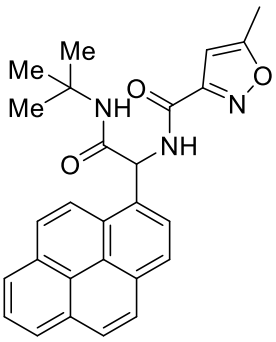
4b

***N*-(2-(*Tert*-butylamino)-2-oxo-1-(pyren-1-yl)ethyl)pyrazine-2-carboxamide (4c):** The compound **4c** was obtained after purification by column chromatography on silica gel (EtOAc:hexane = 30:70) as a brown-coloured solid (33 mg, 15%, 0.5 mmol scale); R_f (50% EtOAc/hexane) 0.25; mp: 180-182 ^oC; IR (DCM): 3331, 2974, 1667, 1510, 748 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ_H 9.29 (1H, d, J = 7.1 Hz), 9.16 (1H, d, J = 1.3 Hz), 8.57-8.55 (2H, m), 8.40-8.39 (1H, m), 8.25-8.17 (5H, m), 8.09-7.99 (3H, m), 6.55 (1H, d, J = 7.2 Hz), 5.78 (1H, s), 1.29 (9H, s); $^{13}C\{^1H\}$ NMR (~101 MHz, $CDCl_3$): δ_C 169.2, 162.5, 147.1, 144.1, 144.0, 142.6, 131.6, 131.1, 131.1, 130.5, 128.9, 128.8, 128.0, 127.3, 126.5, 126.2, 125.7, 125.5, 125.2, 125.2, 124.6, 122.4, 55.2, 52.0, 28.5; HRMS (ESI): *m/z* $[M+H]^+$ calcd for $C_{27}H_{25}N_4O_2$: 437.1978 found, 437.1984.



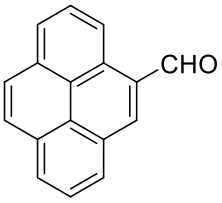
4c

***N*-(2-(*Tert*-butylamino)-2-oxo-1-(pyren-1-yl)ethyl)-5-methylisoxazole-3-carboxamide (4d):** The compound **4d** was obtained after purification by column chromatography on silica gel (EtOAc:hexane = 30:70) as a brown-coloured solid (68 mg, 31%, 0.5 mmol scale); R_f (50% EtOAc/hexane) 0.25; mp: 228-230 ^oC; IR (DCM): 3344, 2926, 1673, 1528, 755 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ_H 8.48 (1H, d, J = 9.3 Hz), 8.34 (1H, d, J = 6.5 Hz), 8.25-8.04 (8H, m), 6.42 (1H, d, J = 6.6 Hz), 6.34 (1H, s), 5.38 (1H, s), 2.43 (3H, s), 1.26 (9H, s); $^{13}C\{^1H\}$ NMR (~101 MHz, $CDCl_3$): δ_C 171.0, 168.8, 158.8, 158.3, 131.7, 131.2, 130.8, 130.6, 128.9, 128.8, 128.1, 127.3, 126.7, 126.3, 125.8, 125.6, 125.3, 125.3, 124.7, 122.3, 101.3, 55.4, 52.1, 28.5, 12.3; HRMS (ESI): *m/z* $[M+H]^+$ calcd for $C_{27}H_{26}N_3O_3$: 440.1974 found, 440.1968.



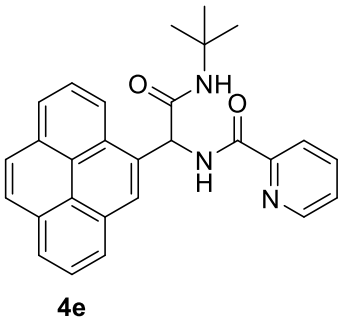
4d

Pyrene-4-carbaldehyde (3d):[24] The compound **3d** was obtained after purification by column chromatography on silica gel (EtOAc:hexane = 05:95) as a yellow-coloured solid (197 mg, 86%, 1 mmol scale); R_f (20% EtOAc/hexane) 0.8; mp: 157-159 ^oC; IR (DCM): 2972, 1659, 1510, 729, 512 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ_H 10.43 (1H, s), 9.54 (1H, d, J = 7.9 Hz), 8.40 (1H, s), 8.27-8.19 (3H, m), 8.10-7.98 (4H, m); $^{13}C\{^1H\}$ NMR (~101 MHz, $CDCl_3$): δ_C 193.8, 141.7, 131.1, 131.0, 131.0, 129.2, 128.6, 128.3, 127.3, 127.2, 126.9, 126.6, 126.3, 126.3, 125.9, 125.1, 123.6; HRMS (ESI): *m/z* $[M+H]^+$ calcd for $C_{17}H_{11}O$: 231.0810 found, 231.0799.



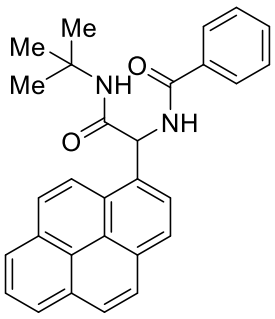
3d

***N*-(2-(*Tert*-butylamino)-2-oxo-1-(pyren-4-yl)ethyl)picolinamide (4e):** The compound **4e** was obtained after purification by column chromatography on silica gel (EtOAc:hexane = 30:70) as a yellow-coloured solid (126 mg, 58%, 0.5 mmol scale); R_f (50% EtOAc/hexane) 0.25; mp: 215-217 ^oC; IR (DCM): 3337, 2971, 1665, 1510, 722 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ_H 9.45 (1H, d, J = 7.1 Hz), 8.60 (1H, d, J = 7.8 Hz), 8.52 (1H, d, J = 4.3 Hz), 8.39 (1H, s), 8.24-8.19 (3H, m), 8.09-8.01 (5H, m), 7.72-7.68 (1H, m), 7.34-7.31 (1H, m), 6.45 (1H, d, J = 7.2 Hz), 5.91 (1H, s), 1.30 (9H, s); $^{13}C\{^1H\}$ NMR (~101 MHz, $CDCl_3$): δ_C 169.3, 164.2, 149.4, 148.2, 137.0, 133.2, 131.6, 130.9, 130.3, 129.2, 128.9, 127.7, 127.2, 126.2, 126.2, 126.1, 125.8, 125.7, 125.6, 125.4, 124.4, 122.1, 121.3, 56.3, 51.9, 28.5; HRMS (ESI): *m/z* $[M+H]^+$ calcd for $C_{28}H_{26}N_3O_2$: 436.2025 found, 436.2022.



4e

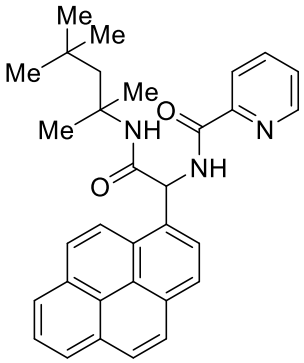
***N*-(2-(*Tert*-butylamino)-2-oxo-1-(pyren-1-yl)ethyl)benzamide (4f):** The compound **4f** was obtained after purification by column chromatography on silica gel (EtOAc:hexane = 30:70) as a yellow-coloured solid (34 mg, 40%, 0.2 mmol scale); R_f (50% EtOAc/hexane) 0.25; mp: 157-159 ^oC; IR (DCM): 3339, 1658, 1508, 907, 724 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ_H 8.57 (1H, d, J = 9.3 Hz), 8.25-8.21 (5H, m), 8.14-8.04 (3H, m), 7.93 (1H, d, J = 6.1 Hz), 7.86-7.83 (2H, m), 7.49-7.45 (1H, m), 7.41-7.37 (2H, m), 6.48 (1H, d, J = 6.2 Hz), 5.46 (1H, s), 1.26 (9H, s); $^{13}C\{^1H\}$ NMR (~101 MHz, $CDCl_3$): δ_C 169.8, 166.9, 133.8, 131.7, 131.6, 131.6, 131.3, 130.7, 128.9, 128.8, 128.5, 128.0, 127.4, 127.2, 126.7, 126.3, 125.7, 125.5, 125.4, 125.3, 124.8, 122.5, 55.7, 52.1, 28.5; HRMS (ESI): *m/z* $[M+H]^+$ calcd for $C_{29}H_{27}N_2O_2$: 435.2073 found, 435.2065.



4f

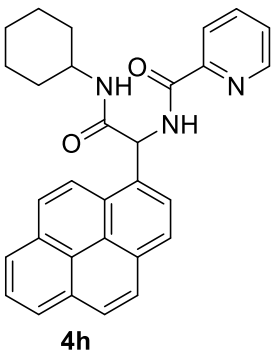
***N*-(2-Oxo-1-(pyren-1-yl)-2-((2,4,4-trimethylpentan-2-yl)amino)ethyl)picolinamide (4g):** The compound **4g** was obtained after purification by column chromatography on silica gel (EtOAc:hexane = 30:70) as a brown-coloured solid (250 mg, 51%, 1 mmol scale); R_f (50% EtOAc/hexane) 0.25; mp: 178-180 ^oC; IR (DCM): 3335, 2958, 1671, 1513, 840 cm^{-1};

^{1}H NMR (400 MHz, $CDCl_3$): δ_H 9.57 (1H, d, J = 6.6 Hz), 8.57-8.55 (2H, m), 8.26-8.19 (5H, m), 8.10-8.06 (3H, m), 8.02 (1H, t, J = 7.6 Hz), 7.74 (1H, t, J = 7.7 Hz), 7.37-7.34 (1H, m), 6.50 (1H, d, J = 6.8 Hz), 5.67 (1H, s), 1.66 (1H, d, J = 14.9 Hz), 1.48 (1H, d, J = 14.9 Hz), 1.40 (3H, s), 1.32 (3H, s), 0.69 (9H, s); ^{13}C{^{1}H} NMR (~101 MHz, $CDCl_3$): δ_C 168.9, 164.1, 149.5, 148.3, 137.1, 131.5, 131.4, 131.2, 130.6, 128.9, 128.7, 127.8, 127.3, 126.7, 126.2, 126.1, 125.6, 125.4, 125.3, 125.2, 124.7, 122.5, 122.1, 55.9, 52.6, 31.3, 31.1, 28.9, 28.0; HRMS (ESI): *m/z* $[M+H]^+$ calcd for $C_{32}H_{34}N_3O_2$: 492.2651 found, 492.2655.



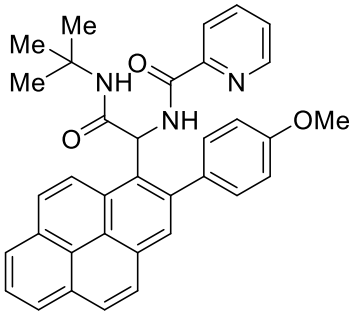
4g

***N*-(2-(Cyclohexylamino)-2-oxo-1-(pyren-1-yl)ethyl)picolinamide (4h):** The compound **4h** was obtained after purification by column chromatography on silica gel (EtOAc:hexane = 30:70) as a brown-coloured solid (267 mg, 58%, 1 mmol scale); R_f (50% EtOAc/hexane) 0.25; mp: 214-216 ^{o}C; IR (DCM): 2982, 1663, 1515, 614 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 9.42 (1H, d, J = 7.2 Hz), 8.58 (1H, d, J = 9.2 Hz), 8.45 (1H, s), 8.26 (1H, d, J = 8.0 Hz), 8.19-8.10 (4H, m), 8.05-7.96 (4H, m), 7.62-7.61 (1H, m), 7.25-7.24 (1H, m), 6.74-6.71 (1H, m), 6.24-6.21 (1H, m), 3.89-3.82 (1H, m), 1.91-1.88 (1H, m), 1.73-1.71 (1H, m), 1.58-1.46 (3H, m), 1.30-1.17 (2H, m), 1.07-0.78 (3H, m); ^{13}C{^{1}H} NMR (~101 MHz, $CDCl_3$): δ_C 169.3, 164.0, 149.2, 148.1, 136.8, 131.3, 131.1, 130.5, 128.9, 128.6, 127.7, 127.2, 126.2, 126.1, 126.0, 125.4, 125.3, 125.1, 125.1, 124.5, 122.5, 122.0, 54.9, 48.8, 32.6, 32.4, 25.2, 24.7, 24.5; HRMS (ESI): *m/z* $[M+H]^+$ calcd for $C_{30}H_{28}N_3O_2$: 462.2182 found, 462.2180.



4h

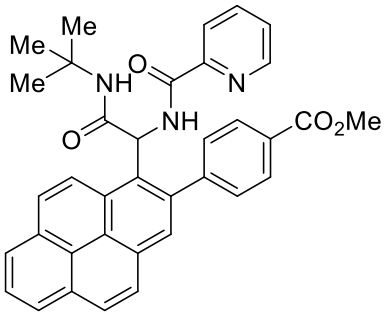
***N*-(2-(*Tert*-butylamino)-1-(2-(4-methoxyphenyl)pyren-1-yl)-2-oxoethyl)picolinamide (6a):** The compound **6a** was obtained after purification by column chromatography on silica gel (EtOAc:hexane = 30:70) as a brown-coloured solid (41 mg, 76%, 0.1 mmol scale); R_f (50% EtOAc/hexane) 0.3; mp: 139-140 ^{o}C; IR (DCM): 3381, 2959, 1682, 1513, 764 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 9.62 (1H, d, J = 5.4 Hz), 8.59 (1H, d, J = 4.6 Hz), 8.53 (1H, d, J = 9.4 Hz), 8.22-8.18 (4H, m), 8.14-8.00 (6H, m), 7.75 (1H, td, J_1 = 7.7, J_2 = 1.6 Hz), 7.39-7.36 (1H, m), 7.14 (2H, d, J = 8.1 Hz), 6.43 (1H, d, J = 6.0 Hz), 5.47 (1H, s), 3.95



6a

(3H, s), 1.22 (9H, s); $^{13}C\{^{1}H\}$ NMR (~101 MHz, $CDCl_3$): δ_C 169.6, 163.8, 159.3, 149.7, 148.3, 141.0, 137.1, 134.0, 131.1, 131.0, 130.5, 129.5, 129.1, 128.7, 128.3, 127.4, 127.2, 126.1, 125.6, 125.5, 125.0, 124.7, 123.9, 122.1, 114.0, 55.4, 55.2, 51.8, 28.5; HRMS (ESI): *m/z* $[M+H]^+$ calcd for $C_{35}H_{32}N_3O_3$: 542.2444 found, 542.2423.

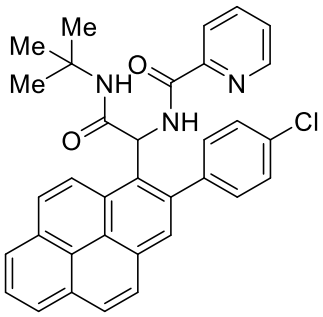
Methyl 4-(1-(2-(*tert*-butylamino)-2-oxo-1-(picolinamido)ethyl)pyren-2-yl)benzoate (6b):



6b

The compound **6b** was obtained after purification by column chromatography on silica gel (EtOAc:hexane = 30:70) as a brown-coloured solid (39 mg, 69%, 0.1 mmol scale); R_f (50% EtOAc/hexane) 0.3; mp: 120-122 ºC; IR (DCM): 3359, 2962, 1674, 1503, 751 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 9.55 (1H, br. s), 8.56 (1H, d, J = 4.5 Hz), 8.51 (1H, d, J = 9.4 Hz), 8.28-8.21 (6H, m), 8.14-8.02 (6H, m), 7.77 (1H, td, J_1 = 7.6, J_2 = 1.5 Hz), 7.41-7.38 (1H, m), 6.31 (1H, d, J = 5.9 Hz), 5.55 (1H, s), 4.01 (3H, s), 1.25 (9H, s); $^{13}C\{^{1}H\}$ NMR (~101 MHz, $CDCl_3$): δ_C 169.3, 167.0, 163.5, 149.2, 148.0, 146.6, 140.3, 137.5, 131.1, 131.1, 130.5, 129.8, 129.8, 129.6, 129.2, 129.1, 128.8, 128.6, 127.1, 126.6, 126.4, 126.3, 125.9, 125.7, 125.2, 124.6, 123.6, 122.3, 55.2, 52.3, 51.9, 28.5; HRMS (ESI): *m/z* $[M+H]^+$ calcd for $C_{36}H_{32}N_3O_4$: 570.2393 found, 570.2404.

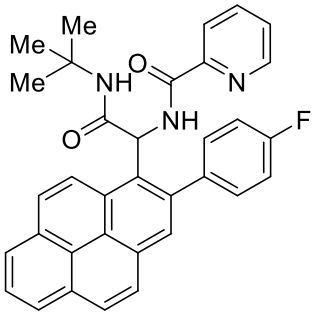
***N*-(2-(*Tert*-butylamino)-1-(2-(4-chlorophenyl)pyren-1-yl)-2-oxoethyl)picolinamide (6c):**



6c

The compound **6c** was obtained after purification by column chromatography on silica gel (EtOAc:hexane = 30:70) as a brown-coloured solid (26 mg, 48%, 0.1 mmol scale); R_f (50% EtOAc/hexane) 0.3; mp: 112-114 ºC; IR (DCM): 3359, 2963, 1676, 1502, 754 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 9.56 (1H, d, J = 5.6 Hz), 8.59-8.57 (1H, m), 8.49 (1H, d, J = 9.4 Hz), 8.24-8.20 (4H, m), 8.14-8.03 (6H, m), 7.77 (1H, td, J_1 = 7.7, J_2 = 1.7 Hz), 7.57 (2H, d, J = 7.6 Hz), 7.41-7.37 (1H, m), 6.32 (1H, d, J = 5.9 Hz), 5.47 (1H, s), 1.23 (9H, s); $^{13}C\{^{1}H\}$ NMR (~101 MHz, $CDCl_3$): δ_C 169.4, 163.8, 149.5, 148.3, 140.2, 140.1, 137.1, 134.1, 131.1, 131.1, 130.5, 129.2, 129.1, 129.0, 128.8, 128.8, 128.5, 127.1, 127.0, 126.3, 126.2, 125.8, 125.7, 125.2, 124.6, 123.6, 122.1, 55.1, 51.9, 28.5; HRMS (ESI): *m/z* $[M+H]^+$ calcd for $C_{34}H_{29}ClN_3O_2$: 546.1948 found, 546.1942.

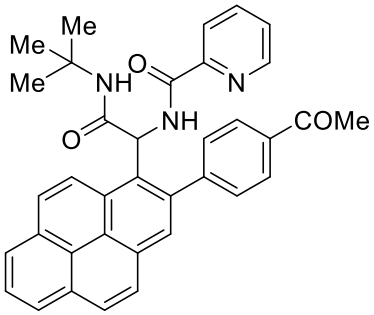
***N*-(2-(*Tert*-butylamino)-1-(2-(4-fluorophenyl)pyren-1-yl)-2-oxoethyl)picolinamide (6d):**



6d

The compound **6d** was obtained after purification by column chromatography on silica gel (EtOAc:hexane = 30:70) as a brown-coloured solid (36 mg, 68%, 0.1 mmol scale); R_f (50% EtOAc/hexane) 0.3; mp: 192-194 ^oC; IR (DCM): 2964, 1675, 1507, 1224, 845 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ_H 9.57 (1H, d, J = 5.6 Hz), 8.59-8.57 (1H, m), 8.49 (1H, d, J = 9.4 Hz), 8.24-8.19 (4H, m), 8.13 (2H, d, J = 8.7 Hz), 8.08-8.02 (4H, m), 7.76 (1H, td, J_1 = 7.7, J_2 = 1.7 Hz), 7.41-7.37 (1H, m), 7.31-7.26 (2H, m), 6.34 (1H, d, J = 6.0 Hz), 5.47 (1H, s), 1.23 (9H, s); $^{13}C\{^1H\}$ NMR (~101 MHz, $CDCl_3$): δ_C 169.5, 163.8, 162.6 (d, J_{C-F} = 246.4 Hz), 149.5, 148.3, 140.3, 137.6 (d, J_{C-F} = 3.3 Hz), 137.1, 131.1, 131.1, 130.1, 130.5, 129.2, 129.2, 128.9, 128.5, 127.2, 127.1, 126.3, 126.2, 125.8, 125.7 (d, J_{C-F} = 12.4 Hz), 125.1, 124.6, 123.6, 122.1, 55.1, 51.8, 28.5; ^{19}F NMR (~376 MHz, $CDCl_3$): δ = –114.37; HRMS (ESI): *m/z* $[M+H]^+$ calcd for $C_{34}H_{29}FN_3O_2$: 530.2244 found, 530.2242.

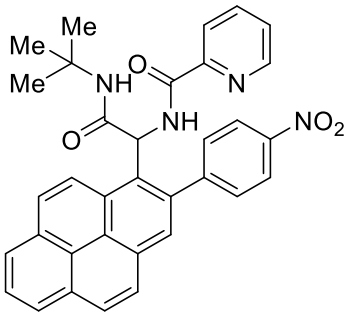
***N*-(1-(2-(4-Acetylphenyl)pyren-1-yl)-2-(*tert*-butylamino)-2-oxoethyl)picolinamide (6e):**



6e

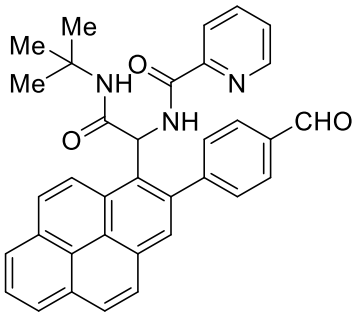
The compound **6e** was obtained after purification by column chromatography on silica gel (EtOAc:hexane = 30:70) as a brown-coloured solid (21 mg, 38%, 0.1 mmol scale); R_f (30% EtOAc/hexane) 0.5; mp: 130-132 ^oC; IR (DCM): 3358, 2925, 1676, 1506, 752 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ_H 9.55 (1H, d, J = 5.4 Hz), 8.56 (1H, d, J = 4.7 Hz), 8.50 (1H, d, J = 9.4 Hz), 8.24-8.18 (6H, m), 8.13-8.01 (6H, m), 7.75 (1H, td, J_1 = 7.7, J_2 = 1.4 Hz), 7.39-7.36 (1H, m), 6.30 (1H, d, J = 5.4 Hz), 5.54 (1H, s), 2.73 (3H, s), 1.25 (9H, s); $^{13}C\{^1H\}$ NMR (~101 MHz, $CDCl_3$): δ_C 197.9, 169.3, 163.8, 149.4, 148.3, 146.7, 140.2, 137.1, 136.3, 131.1, 130.4, 129.2, 129.1, 128.8, 128.6, 127.1, 126.6, 126.4, 126.2, 125.9, 125.7, 125.2, 124.6, 123.5, 122.1, 55.2, 51.9, 28.5, 26.8; HRMS (ESI): *m/z* $[M+H]^+$ calcd for $C_{36}H_{32}N_3O_3$: 554.2444 found, 554.2443.

***N*-(2-(*Tert*-butylamino)-1-(2-(4-nitrophenyl)pyren-1-yl)-2-oxoethyl)picolinamide (6f):**



6f

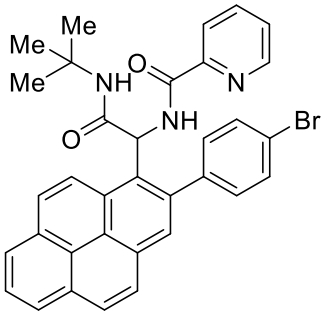
The compound **6f** was obtained after purification by column chromatography on silica gel (EtOAc:hexane= 30:70) as a brown-coloured solid (40 mg, 72%, 0.1 mmol scale); R_f (50% EtOAc/hexane) 0.2; mp: 138-140 ^oC; IR (DCM): 3361, 3071, 1677, 1510, 750 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ_H 9.47 (1H, d, J = 5.8 Hz), 8.55 (1H, d, J = 4.6 Hz), 8.48-8.42 (3H, m), 8.28-8.23 (4H. m), 8.14 (1H, d, J = 8.9 Hz), 8.09-8.04 (5H, m), 7.77 (1H, td, J_1 = 7.7, J_2 = 1.1 Hz), 7.41-7.38 (1H, m), 6.27 (1H, d, J = 6.1 Hz), 5.62 (1H, s), 1.28 (9H, s); $^{13}C\{^1H\}$ NMR (~101 MHz, $CDCl_3$): δ_C 169.3, 164.0, 149.2, 148.7, 148.4, 147.5, 139.1, 137.3, 131.2, 131.2, 130.5, 129.5, 129.3, 128.9, 128.6, 127.0, 126.6, 126.4, 126.4, 126.1, 126.0, 125.4, 124.5, 123.7, 123.7, 123.2, 122.2, 55.1, 52.0, 28.5; HRMS (ESI): *m/z* $[M+H]^+$ calcd for $C_{34}H_{29}N_4O_4$: 557.2189 found, 557.2175.



6g

***N*-(2-(*Tert*-butylamino)-1-(2-(4-formylphenyl)pyren-1-yl)-2-oxoethyl)picolinamide (6g):** The compound **6g** was obtained after purification by column chromatography on silica gel (EtOAc:hexane = 30:70) as a brown-coloured solid (35 mg, 66%, 0.1 mmol scale); R_f (50% EtOAc/hexane) 0.3; mp: 135-137 ^oC; IR (DCM): 3362, 3015, 1681, 1504, 744 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ_H 10.18 (1H, s), 9.52 (1H, d, J = 5.6 Hz), 8.55 (1H, d, J = 4.7 Hz), 8.49 (1H, d, J = 9.3 Hz), 8.25-8.22 (4H, m), 8.14-8.03 (8H, m), 7.78-7.74 (1H, m), 7.40-7.36 (1H, m), 6.30 (1H, d, J = 5.6 Hz), 5.56 (1H, br. s), 1.25 (9H, s); $^{13}C\{^1H\}$ NMR (~101 MHz, $CDCl_3$): δ_C 192.1, 169.4, 163.9, 149.4, 148.3, 148.2, 140.1, 137.2, 135.6, 131.2, 130.5, 129.3, 129.2, 128.7, 128.7, 127.1, 126.5, 126.5, 126.3, 126.0, 125.8, 125.3, 124.6, 123.5, 122.1, 55.1, 51.9, 28.5; HRMS (ESI): *m/z* $[M+H]^+$ calcd for $C_{35}H_{30}N_3O_3$: 540.2287 found, 540.2299.

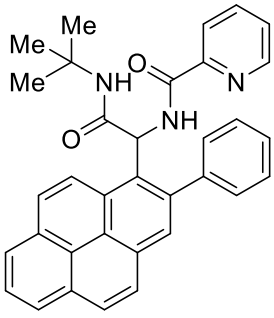
***N*-(1-(2-(4-Bromophenyl)pyren-1-yl)-2-(*tert*-butylamino)-2-oxoethyl)picolinamide (6h):**



6h

The compound **6h** was obtained after purification by column chromatography on silica gel (EtOAc:hexane = 30:70) as a brown-coloured solid (47 mg, 80%, 0.1 mmol scale); R_f (50% EtOAc/hexane) 0.3; mp: 142-144 ^oC; IR (DCM): 3401, 2930, 1679, 1506, 759 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ_H 9.56 (1H, d, J = 5.4 Hz), 8.58 (1H, d, J = 4.7 Hz), 8.50 (1H, d, J = 9.4 Hz), 8.23-8.20 (4H, m), 8.13-8.02 (6H, m), 7.78-7.72 (3H, m), 7.40-7.37 (1H, m), 6.33 (1H, d, J = 5.9 Hz), 5.49 (1H, s), 1.24 (9H, s); $^{13}C\{^1H\}$ NMR (~101 MHz, $CDCl_3$): δ_C 169.4, 163.7, 149.3, 148.2, 140.7, 140.1, 137.3, 131.7, 131.7, 131.1, 131.1, 130.5, 129.2, 129.0, 129.0, 128.5, 127.1, 126.9, 126.3, 126.3, 125.8, 125.7, 125.2, 124.6, 123.6, 122.3, 122.2, 55.2, 51.9, 28.5; HRMS (ESI): *m/z* $[M+H]^+$ calcd for $C_{34}H_{29}BrN_3O_2$: 590.1443 found, 590.1443.

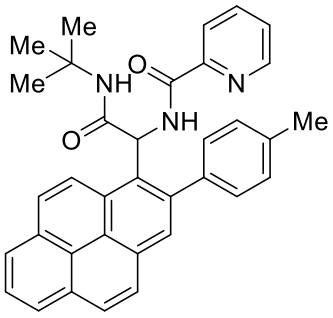
***N*-(2-(*Tert*-butylamino)-2-oxo-1-(2-phenylpyren-1-yl)ethyl)picolinamide (6i):** The



6i

compound **6i** was obtained after purification by column chromatography on silica gel (EtOAc:hexane = 30:70) as a brown-coloured solid (29 mg, 57%, 0.1 mmol scale); R_f (50% EtOAc/hexane) 0.3; mp: 220-222 ^oC; IR (DCM): 3398, 3007, 1675, 1503, 749 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ_H 9.62 (1H, d, J = 4.9 Hz), 8.59-8.55 (2H, m), 8.22-8.19 (3H, m), 8.16 (1H, s), 8.12-8.01 (5H, m), 7.75 (1H, td, J_1 = 7.7, J_2 = 1.5 Hz), 7.62-7.53 (4H, m), 7.39-7.36 (1H, m), 6.39 (1H, d, J = 5.6 Hz), 5.50 (1H, s), 1.23 (9H, s); $^{13}C\{^1H\}$ NMR (~101 MHz, $CDCl_3$): δ_C 169.5, 163.7, 149.7, 148.3, 141.8, 141.3, 137.1, 131.1, 131.0, 130.5, 129.2, 129.2, 128.8, 128.6, 128.3, 127.9, 127.2, 127.1, 126.2, 126.1, 125.7, 125.6, 125.1, 124.7, 123.9, 122.1, 55.2, 51.8, 28.5; HRMS (ESI): *m/z* $[M+H]^+$ calcd for $C_{34}H_{30}N_3O_2$: 512.2338 found, 512.2328.

***N*-(2-(*Tert*-butylamino)-2-oxo-1-(2-(*p*-tolyl)pyren-1-yl)ethyl)picolinamide (6j):** The

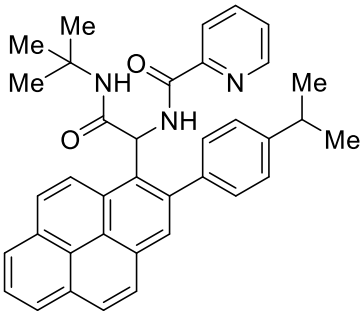


6j

compound **6j** was obtained after purification by column chromatography on silica gel (EtOAc:hexane = 30:70) as a brown-coloured solid (26 mg, 50%, 0.1 mmol scale); R_f (50% EtOAc/hexane) 0.3; mp: 182-184 ^oC; IR (DCM): 3399, 3011, 1676, 1504, 745 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ_H 9.62 (1H, d, J = 5.4 Hz), 8.59-8.54 (2H, m), 8.22-8.00 (10H, m), 7.75 (1H, td, J_1 = 7.7, J_2 = 1.4 Hz), 7.43-7.35 (3H, m), 6.41 (1H, d, J = 5.9

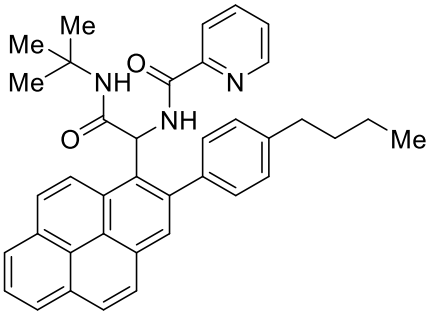
Hz), 5.49 (1H, s), 2.53 (3H, s), 1.23 (9H, s); $^{13}C\{^{1}H\}$ NMR (~101 MHz, $CDCl_3$): δ_C 169.6, 163.7, 149.7, 148.3, 141.4, 138.8, 137.6, 137.1, 131.1, 131.0, 130.5, 129.3, 129.1, 128.7, 128.3, 127.2, 126.2, 126.1, 125.6, 125.5, 125.0, 124.7, 123.9, 122.1, 55.2, 51.8, 28.5, 21.4; HRMS (ESI): *m/z* $[M+H]^+$ calcd for $C_{35}H_{32}N_3O_2$: 526.2495 found, 526.2507.

***N*-(2-(*Tert*-butylamino)-1-(2-(4-isopropylphenyl)pyren-1-yl)-2-oxoethyl)picolinamide (6k):** The compound **6k** was obtained after purification by column chromatography on silica gel (EtOAc:hexane = 30:70) as a brown-coloured solid (21 mg, 38%, 0.1 mmol scale); R_f (50% EtOAc/hexane) 0.3; mp: 106-108 ^{o}C; IR (DCM): 2966, 2923, 1678, 1509, 838 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 9.61 (1H, d, J = 5.2 Hz), 8.58 (1H, d, J = 5.5 Hz), 8.53 (1H, d, J = 9.4 Hz), 8.22-8.01 (10H, m), 7.75 (1H, td, J_1 = 7.7, J_2 = 1.7 Hz), 7.46-7.44 (2H, m), 7.40-7.37 (1H, m), 6.40 (1H, d, J = 5.8 Hz), 5.46 (1H, s), 3.09-3.06 (1H, m), 1.39 (6H, d, J = 6.9 Hz), 1.21 (9H, s); $^{13}C\{^{1}H\}$ NMR (~101 MHz, $CDCl_3$): δ_C 169.5, 163.7, 149.8, 148.4, 148.3, 141.4, 139.1, 137.0, 131.1, 131.0, 130.5, 129.3, 129.1, 128.6, 128.2, 127.4, 127.3, 127.3, 126.1, 126.1, 125.6, 125.5, 125.0, 124.7, 123.9, 122.0, 55.2, 51.8, 33.9, 28.5, 24.0; HRMS (ESI): *m/z* $[M+H]^+$ calcd for $C_{37}H_{36}N_3O_2$: 554.2808 found, 554.2817.



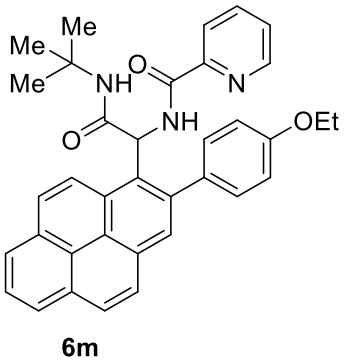
6k

***N*-(2-(*Tert*-butylamino)-1-(2-(4-butylphenyl)pyren-1-yl)-2-oxoethyl)picolinamide (6l):** The compound **6l** was obtained after purification by column chromatography on silica gel (EtOAc:hexane = 30:70) as a brown-coloured solid (31 mg, 55%, 0.1 mmol scale); R_f (50% EtOAc/hexane) 0.4; mp: 125-127 ^{o}C; IR (DCM): 3407, 3015, 1677, 1508, 743 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 9.63 (1H, d, J = 5.1 Hz), 8.59 (1H, d, J = 4.7 Hz), 8.56 (1H, d, J = 9.4 Hz), 8.22-8.16 (4H, m), 8.11-8.00 (5H, m), 7.75 (1H, td, J_1 = 7.7, J_2 = 1.6 Hz), 7.44-7.36 (4H, m), 6.43 (1H, d, J = 5.8 Hz), 5.49 (1H, s), 2.79 (2H, t, J = 7.8 Hz), 1.79-1.74 (2H, m), 1.52-1.46 (2H, m), 1.22 (9H, s), 1.03 (3H, t, J = 7.4 Hz); $^{13}C\{^{1}H\}$ NMR (~101 MHz, $CDCl_3$): δ_C 169.5, 163.7, 149.7, 148.3, 142.5, 141.4, 139.0, 137.1, 131.1, 131.0, 130.5, 130.2, 129.3, 129.1, 128.7, 128.3, 127.3, 127.2, 126.1, 126.1, 125.6, 125.5, 125.0, 124.7, 123.9, 122.0, 55.2, 51.8, 35.5, 33.6, 28.5, 22.5, 14.1; HRMS (ESI): *m/z* $[M+H]^+$ calcd for $C_{38}H_{38}N_3O_2$: 568.2964 found, 568.2965.



6l

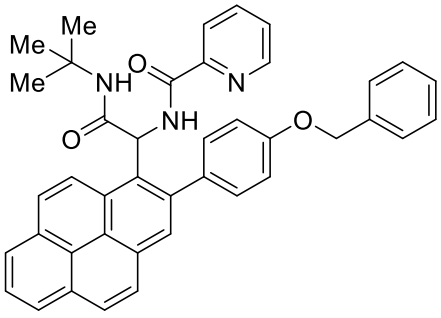
***N*-(2-(*Tert*-butylamino)-1-(2-(4-ethoxyphenyl)pyren-1-yl)-2-oxoethyl)picolinamide (6m):**



6m

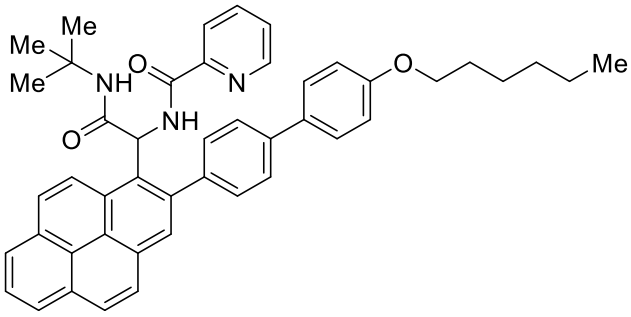
The compound **6m** was obtained after purification by column chromatography on silica gel (EtOAc:hexane= 30:70) as a brown-coloured solid (34 mg, 62%, 0.1 mmol scale); R_f (50% EtOAc/hexane) 0.3; mp: 118-120 ^oC; IR (DCM): 3397, 2977, 1675, 1503, 749 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ_H 9.62 (1H, d, J = 5.3 Hz), 8.59 (1H. dd, J_1 = 4.7, J_2 = 0.6 Hz), 8.52 (1H, d, J = 9.4 Hz), 8.22-8.00 (10H, m), 7.76 (1H, td, J_1 = 7.7, J_2 = 1.7 Hz), 7.40-7.37 (1H, m), 7.12 (2H, d, J = 8.2 Hz), 6.42 (1H, d, J = 5.8 Hz), 5.45 (1H, s), 4.18 (2H, q, J = 7.0 Hz), 1.52 (3H, t, J = 7.0 Hz), 1.21 (9H, s); $^{13}C\{^1H\}$ NMR (~101 MHz, $CDCl_3$): δ_C 169.5, 163.7, 158.7, 149.7, 148.3, 141.1, 137.1, 133.8, 131.1, 131.0, 130.5, 129.5, 129.1, 128.7, 128.2, 127.4, 127.2, 126.1, 125.6, 125.5, 125.0, 124.7, 123.9, 122.0, 114.5, 63.6, 55.2, 51.7, 28.5, 15.0; HRMS (ESI): *m/z* $[M+H]^+$ calcd for $C_{38}H_{34}N_3O_3$: 556.2600 found, 556.2604.

***N*-(1-(2-(4-(Benzyloxy)phenyl)pyren-1-yl)-2-(*tert*-butylamino)-2-oxoethyl)picolinamide (6n):** The compound **6n** was obtained after purification by column chromatography on silica gel (EtOAc:hexane = 30:70) as a brown-coloured solid (31 mg, 50%, 0.1 mmol scale); R_f (50% EtOAc/hexane) 0.3; mp: 209-211 ^oC; IR (DCM): 3395, 2969, 1675, 1504, 748 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ_H 9.63 (1H, d, J = 5.3 Hz), 8.59 (1H, d, J = 4.7 Hz), 8.54 (1H, d, J = 9.4 Hz), 8.22-8.00 (10H, m), 7.75 (1H, td, J_1 = 7.7, J_2 = 1.6 Hz), 7.55 (2H, d, J = 7.3 Hz), 7.49-7.45 (2H, m), 7.41-7.36 (2H, m), 7.22 (2H, d, J = 7.9 Hz), 6.44 (1H, d, J = 5.8 Hz), 5.47 (1H, s), 5.22 (2H, s), 1.22 (9H, s); $^{13}C\{^1H\}$ NMR (~101 MHz, $CDCl_3$): δ_C 169.5, 163.8, 158.5, 149.7, 148.3, 141.0, 137.1, 136.9, 134.2, 131.1, 131.0, 130.5, 129.5, 129.1, 128.7, 128.3, 128.1, 127.7, 127.4, 127.2, 126.1, 125.6, 125.5, 125.0, 124.7, 123.9, 122.1, 114.9, 70.2, 55.2, 51.8, 28.5; HRMS (ESI): *m/z* $[M+H]^+$ calcd for $C_{41}H_{36}N_3O_3$: 618.2757 found, 618.2759.



6n

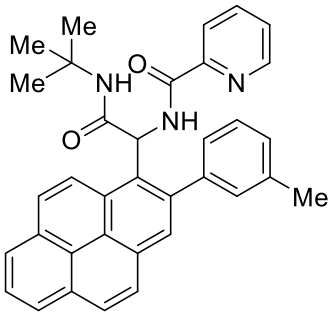
***N*-(2-(*Tert*-butylamino)-1-(2-(4'-(hexyloxy)-[1,1'-biphenyl]-4-yl)pyren-1-yl)-2-oxoethyl)picolinamide (6o):** The compound **6o** was obtained after purification by column



6o

chromatography on silica gel (EtOAc:hexane = 30:70) as a brown-coloured solid (42 mg, 62%, 0.1 mmol scale); R_f (50% EtOAc/hexane) 0.3; mp: 190-192 ^oC; IR (DCM): 3398, 2941, 1679, 1505, 756 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ_H 9.63 (1H, d, J = 5.5 Hz), 8.59-8.58 (1H, m), 8.54 (1H, d, J = 9.4 Hz), 8.23-8.19 (4H, m), 8.14-8.02 (5H, m), 7.80-7.66 (6H, m), 7.40-7.37 (1H, m), 7.06-7.04 (2H, m), 6.44 (1H, d, J = 5.8 Hz), 5.50 (1H, s), 4.06 (2H, t, J = 6.6 Hz), 1.88-1.84 (2H, m), 1.53-1.51 (2H, m), 1.42-1.37 (4H, m), 1.22 (9H, s), 0.95 (3H, t, J = 7.0 Hz); $^{13}C\{^1H\}$ NMR (~101 MHz, $CDCl_3$): δ_C 169.5, 163.8, 159.0, 149.7, 148.3, 141.1, 140.3, 140.0, 137.1, 132.9, 131.1, 131.1, 130.5, 129.3, 129.2, 128.8, 128.3, 128.2, 127.2, 126.8, 126.8, 126.8, 126.2, 126.2, 125.7, 125.6, 125.1, 124.7, 123.9, 122.0, 114.9, 68.1, 55.3, 51.8, 31.7, 29.3, 28.5, 25.8, 22.7, 14.1; HRMS (ESI): *m/z* $[M+H]^+$ calcd for $C_{46}H_{46}N_3O_3$: 688.3539 found, 688.3557.

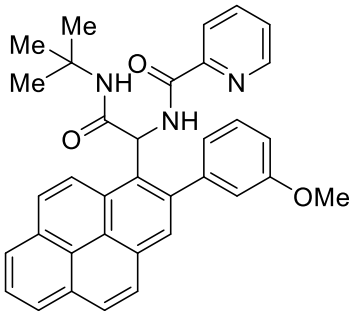
***N*-(2-(*Tert*-butylamino)-2-oxo-1-(2-(*m*-tolyl)pyren-1-yl)ethyl)picolinamide (6p):** The



6p

compound **6p** was obtained after purification by column chromatography on silica gel (EtOAc:hexane = 30:70) as a brown-coloured solid (33 mg, 64%, 0.1 mmol scale); R_f (50% EtOAc/hexane) 0.3; mp: 250-252 ^oC; IR (DCM): 3397, 2962, 1679, 1505, 757 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ_H 9.57 (1H, s), 8.59-8.55 (2H, m), 8.23-8.19 (3H, m), 8.15-8.01 (6H, m), 7.76 (1H, td, J_1 = 7.7, J_2 = 1.6 Hz), 7.50-7.48 (1H, m), 7.40-7.35 (3H, m), 6.41 (1H, d, J =5.6 Hz), 5.52 (1H, s), 2.50 (3H, s), 1.23 (9H, s); $^{13}C\{^1H\}$ NMR (~101 MHz, $CDCl_3$): δ_C 169.5, 163.7, 149.7, 148.3, 141.7, 141.4, 137.1, 131.1, 131.0, 130.5, 129.2, 129.2, 129.1, 128.7, 128.6, 128.3, 127.2, 127.1, 126.2, 126.1, 125.6, 125.5, 125.0, 124.7, 123.9, 122.1, 55.1, 51.7, 28.5, 21.6; HRMS (ESI): *m/z* $[M+H]^+$ calcd for $C_{35}H_{32}N_3O_2$: 526.2495 found, 526.2493.

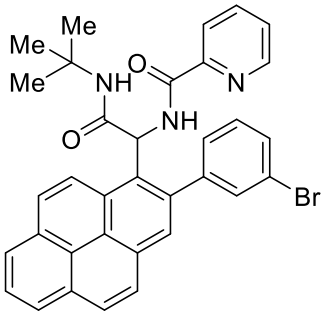
***N*-(2-(*Tert*-butylamino)-1-(2-(3-methoxyphenyl)pyren-1-yl)-2-oxoethyl)picolinamide (6q):** The compound **6q** was obtained after purification by column chromatography on silica



6q

gel (EtOAc:hexane = 30:70) as a brown-coloured solid (24 mg, 46%, 0.1 mmol scale); R_f (50% EtOAc/hexane) 0.3; mp: 222-224 ^{o}C; IR (DCM): 3368, 2965, 1672, 1504, 1219 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 9.64 (1H, br. s), 8.59-8.55 (2H, m), 8.22-8.19 (3H, m), 8.16 (1H, s), 8.11 (1H, d, J = 8.9 Hz), 8.07-8.00 (3H, m), 7.75 (1H, td, J_1 = 7.7, J_2 = 1.6 Hz), 7.56-7.51 (2H, m), 7.39-7.36 (1H, m), 7.09 (2H, d, J = 6.9 Hz), 6.43-6.43 (1H, m), 5.53-5.51 (1H, m), 3.92 (3H, s), 1.23 (9H, s); ^{13}C{^{1}H} NMR (~101 MHz, $CDCl_3$): δ_C 169.5, 163.7, 159.6, 149.7, 148.3, 143.1, 141.1, 137.1, 131.1, 131.0, 130.5, 129.7, 129.2, 129.2, 128.8, 128.7, 128.3, 127.2, 126.9, 126.2, 126.1, 125.7, 125.6, 125.6, 125.1, 124.7, 123.9, 122.0, 115.8, 55.4, 55.1, 51.8, 28.5; HRMS (ESI): *m/z* [M+H]$^{+}$ calcd for $C_{35}H_{32}N_3O_3$: 542.2444 found, 542.2451.

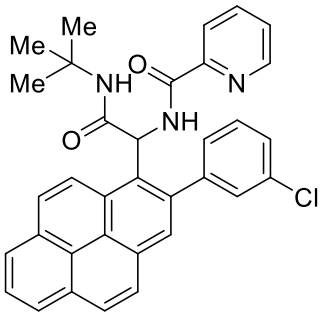
***N*-(1-(2-(3-Bromophenyl)pyren-1-yl)-2-(*tert*-butylamino)-2-oxoethyl)picolinamide (6r):**



6r

The compound **6r** was obtained after purification by column chromatography on silica gel (EtOAc:hexane = 30:70) as a brown-coloured solid (34 mg, 59%, 0.1 mmol scale); R_f (50% EtOAc/hexane) 0.3; mp: 233-235 ^{o}C; IR (DCM): 3409, 3368, 1673, 1504 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 9.55-9.44 (1H, m), 8.59-8.59 (1H, m), 8.52 (1H, d, J = 9.4 Hz), 8.24-8.21 (4H, m), 8.14-8.03 (6H, m), 7.76 (1H, td, J_1 = 7.7, J_2 = 1.6 Hz), 7.67 (1H, d, J = 7.4 Hz), 7.50-7.47 (1H, m), 7.41-7.37 (1H, m), 6.32-6.31 (1H, m), 5.47 (1H, s), 1.25 (9H, s); ^{13}C{^{1}H} NMR (~101 MHz, $CDCl_3$): δ_C 169.3, 163.8, 149.6, 148.4, 143.9, 143.8, 139.7, 137.1, 131.2, 131.1, 130.9, 130.5, 129.3, 129.0, 129.0, 128.5, 127.1, 126.8, 126.3, 126.2, 125.8, 125.7, 125.6, 125.2, 124.6, 123.7, 122.1, 122.1, 55.1 51.9, 28.5; HRMS (ESI): *m/z* [M+H]$^{+}$ calcd for $C_{34}H_{29}BrN_3O_2$: 590.1443 found, 590.1437.

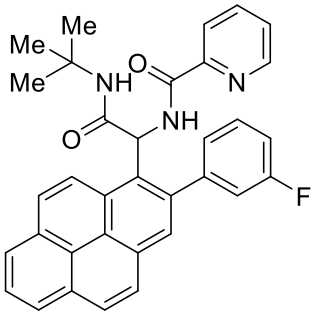
***N*-(2-(*Tert*-butylamino)-1-(2-(3-chlorophenyl)pyren-1-yl)-2-oxoethyl)picolinamide (6s):**



6s

The compound **6s** was obtained after purification by column chromatography on silica gel (EtOAc:hexane = 30:70) as a brown-coloured solid (21 mg, 40%, 0.1 mmol scale); R_f (50% EtOAc/hexane) 0.3; mp: 237-239 ^{o}C; IR (DCM): 3357, 2974, 1675, 1501, 749 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 9.54 (1H, s), 8.59-8.58 (1H, m), 8.53 (1H, d, J = 9.4 Hz), 8.24-8.21 (4H, m), 8.14-8.11 (2H, m), 8.07-8.03 (4H, m), 7.76 (1H, td, J_1 = 7.7, J_2 = 1.5 Hz), 7.53 (2H, m), 7.40-7.37 (1H, m), 6.33-6.32 (1H, m), 5.50 (1H, s), 1.25 (9H, s); ^{13}C{^{1}H} NMR (~101 MHz, $CDCl_3$): δ_C 169.3, 163.8, 149.5, 148.4, 143.5, 139.8, 137.1, 131.2, 131.1, 130.5, 130.0, 130.0, 129.3, 129.0, 128.5, 128.5, 128.0, 127.1, 126.8, 126.4, 126.2, 125.8, 125.7, 125.6, 125.2, 124.6, 123.7, 122.1, 55.1, 51.9, 28.5; HRMS (ESI): *m/z* $[M+H]^+$ calcd for $C_{34}H_{29}ClN_3O_2$: 546.1948 found, 546.1952.

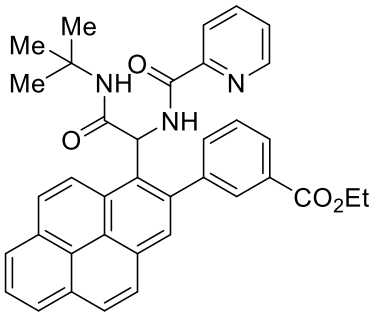
***N*-(2-(*Tert*-butylamino)-1-(2-(3-fluorophenyl)pyren-1-yl)-2-oxoethyl)picolinamide (6t):**[25]



6t

The compound **6t** was obtained after purification by column chromatography on silica gel (EtOAc:hexane = 30:70) as a brown-coloured solid (18 mg, 35%, 0.1 mmol scale); R_f (50% EtOAc/hexane) 0.3; mp: 250-252 ^{o}C; IR (DCM): 3395, 2942, 1682, 1510, 761 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 9.53 (1H, d, J = 5.3 Hz), 8.58 (1H, d, J = 4.7 Hz), 8.51 (1H, d, J = 9.4 Hz), 8.24-8.03 (9H, m), 7.76 (1H, td, J_1 = 7.7, J_2 = 1.7 Hz), 7.57-7.55 (2H, m), 7.41-7.37 (1H, m), 7.24 (1H, td, J_1 = 8.6, J_2 = 2.0 Hz), 6.35 (1H, d, J = 5.7 Hz), 5.50 (1H, s), 1.24 (9H, s); ^{13}C{^{1}H} NMR (~101 MHz, $CDCl_3$): δ_C 169.4, 163.8, 162.6 (d, $J_{C\text{-}F}$ = 246.1 Hz), 149.5, 148.3, 143.9 (d, $J_{C\text{-}F}$ = 7.9 Hz), 140.0 139.9, 139.9, 137.1, 131.1, 131.1, 130.5, 130.1, 129.2, 129.0 (d, $J_{C\text{-}F}$ = 2.5 Hz),128.5, 127.1, 126.8, 126.3, 126.2, 125.8, 125.7, 125.2 124.6, 123.7, 122.1, 114.9 (d, $J_{C\text{-}F}$ = 20.6 Hz), 55.1, 51.8, 28.5; ^{19}F NMR (~376 MHz, $CDCl_3$): δ = –113.1, 111; HRMS (ESI): *m/z* $[M+H]^+$ calcd for $C_{34}H_{29}FN_3O_2$: 530.2244 found, 530.2243.

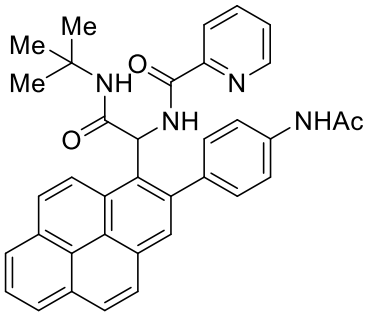
Ethyl 3-(1-(2-(*tert*-butylamino)-2-oxo-1-(picolinamido)ethyl)pyren-2-yl)benzoate (6u):



6u

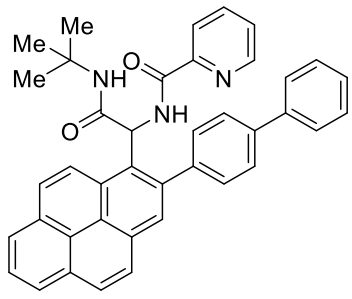
The compound **6u** was obtained after purification by column chromatography on silica gel (EtOAc:hexane = 30:70) as a brown-coloured solid (29 mg, 50%, 0.1 mmol scale); R_f (50% EtOAc/hexane) 0.3; mp: 145-147 ^oC; IR (DCM): 3361, 2977, 1677, 1503, 754 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ_H 9.66 (1H, s), 8.57-8.52 (1H, m), 8.51 (1H, d, J = 9.4 Hz), 8.25-8.12 (8H, m), 8.06-8.02 (3H, m), 7.76-7.71 (2H, m), 7.39-7.36 (1H, m), 6.23 (1H, s), 5.41 (1H, s), 4.44-4.39 (2H, m), 1.39 (3H, t, J = 8.4 Hz), 1.24 (9H, s); $^{13}C\{^1H\}$ NMR (~101 MHz, $CDCl_3$): δ_C 169.4, 166.4, 163.8, 149.6, 148.3, 142.0, 140.4, 137.0, 131.2, 131.1, 130.5, 129.1, 129.0, 129.0, 128.5, 127.2, 127.1, 127.0, 127.0, 126.3, 126.1, 125.8, 125.7, 125.2, 124.6, 123.6, 122.0, 61.1, 55.2, 51.9, 28.5, 14.3; HRMS (ESI): *m/z* $[M+H]^+$ calcd for $C_{37}H_{34}N_3O_4$: 584.2549 found, 584.2545.

***N*-(1-(2-(4-Acetamidophenyl)pyren-1-yl)-2-(*tert*-butylamino)-2-oxoethyl)picolinamide (6v):** The compound **6v** was obtained after purification by column chromatography on silica gel (EtOAc:hexane = 30:70) as a brown-coloured solid (26 mg, 46%, 0.1 mmol scale); R_f (50% EtOAc/hexane) 0.25; mp: 193-195 ^oC; IR (DCM): 3319, 3010, 1671, 1511, 745 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ_H 9.60 (1H, d, J = 5.6 Hz), 8.77-8.50 (4H, m), 8.23-8.01 (10H, m), 7.75-7.69 (2H, m), 7.38-7.35 (1H, m), 6.50 (1H, br. s), 5.51 (1H, s), 1.96 (3H, s), 1.22 (9H, s); $^{13}C\{^1H\}$ NMR (~101 MHz, $CDCl_3$): δ_C 169.6, 169.3, 164.0, 149.3, 148.4, 141.1, 138.5, 138.5, 137.3, 136.7, 131.2, 131.1, 130.4, 129.2, 129.0, 128.8, 128.5, 127.3, 127.2, 126.4, 126.3, 125.8, 125.7, 125.0, 124.6, 123.5, 122.0, 119.7, 55.2, 51.9, 28.5, 24.3; HRMS (ESI): *m/z* $[M+H]^+$ calcd for $C_{36}H_{33}N_4O_3$: 569.2553 found, 569.2556.



6v

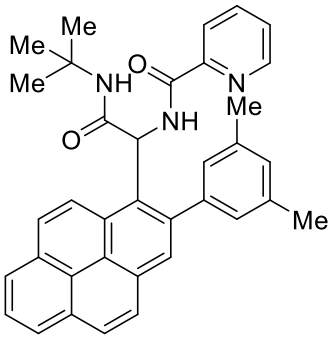
***N*-(1-(2-([1,1'-Biphenyl]-4-yl)pyren-1-yl)-2-(*tert*-butylamino)-2-oxoethyl)picolinamide (6w):** The compound **6w** was obtained after purification by column chromatography on silica gel (EtOAc:hexane = 30:70) as a brown-coloured solid (51 mg, 87%, 0.1 mmol scale); R_f (50% EtOAc/hexane) 0.3; mp: 107-109 ^oC; IR (DCM): 3400, 2926, 1675, 1506, 750 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ_H 9.67 (1H, d, J = 4.8 Hz), 8.60-8.57 (2H, m), 8.24-8.21 (4H, m),



6w

8.13-8.02 (5H, m), 7.86-7.73 (6H, m), 7.57-7.53 (2H, m), 7.46-7.44 (1H, m), 7.39-7.36 (1H, m), 6.49 (1H, d, J = 5.6 Hz), 5.56 (1H, s), 1.26 (9H, s); $^{13}C\{^{1}H\}$ NMR (~101 MHz, $CDCl_3$): δ_C 169.5, 163.8, 149.6, 148.3, 140.9, 140.7, 140.6, 140.6, 137.1, 131.1, 131.1, 130.8, 130.4, 129.2, 129.2, 129.0, 128.9, 128.8, 128.3, 127.5, 127.2, 126.2, 126.1, 125.7, 125.5, 125.1, 124.6, 123.8, 122.0, 55.3, 51.8, 28.5; HRMS (ESI): *m/z* $[M-H]^+$ calcd for $C_{40}H_{32}N_3O_2$: 586.2495 found, 586.2489.

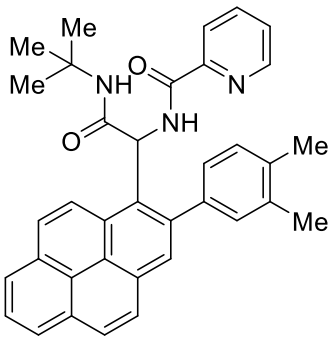
***N*-(2-(*Tert*-butylamino)-1-(2-(3,5-dimethylphenyl)pyren-1-yl)-2-oxoethyl)picolinamide (6x):** The compound **6x** was obtained after purification by column chromatography on silica



6x

gel (EtOAc:hexane = 30:70) as a brown-coloured solid (46 mg, 85%, 0.1 mmol scale); R_f (50% EtOAc/hexane) 0.3; mp: 216-218 ^{o}C; IR (DCM): 3394, 2968, 1776, 1502, 750 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 9.50 (1H, d, J = 5.6 Hz), 8.59-8.57 (2H, m), 8.23-8.19 (3H, m), 8.14-8.01 (6H, m), 7.76 (1H, td, J_1 = 7.7, J_2 = 1.7 Hz), 7.58 (1H, br. s), 7.40-7.36 (1H, m), 7.17 (1H, s), 6.43 (1H, d, J = 5.9 Hz), 5.55 (1H, s), 2.46 (6H, s), 1.23 (9H, s); $^{13}C\{^{1}H\}$ NMR (~101 MHz, $CDCl_3$): δ_C 169.5, 163.6, 149.7, 148.2, 141.6, 141.5, 137.0, 131.1, 130.9, 130.4, 129.4, 129.2, 128.6, 128.2, 127.2, 127.1, 126.1, 126.1, 125.5, 125.4, 124.9, 124.6, 123.9, 122.0, 55.1, 51.6, 28.5, 21.5; HRMS (ESI): *m/z* $[M+H]^+$ calcd for $C_{36}H_{34}N_3O_2$: 540.2651 found, 540.2640.

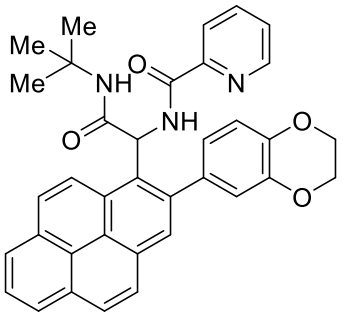
***N*-(2-(*Tert*-butylamino)-1-(2-(3,4-dimethylphenyl)pyren-1-yl)-2-oxoethyl)picolinamide (6y):** The compound **6y** was obtained after purification by column chromatography on silica



6y

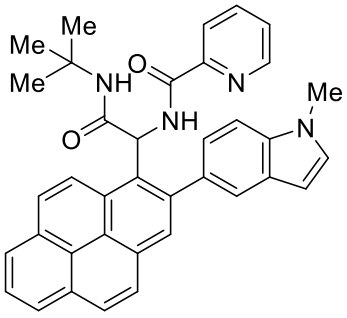
gel (EtOAc:hexane = 30:70) as a brown-coloured solid (29 mg, 55%, 0.1 mmol scale); R_f (50% EtOAc/hexane) 0.3; mp: 130-132 ^{o}C; IR (DCM): 3342, 2928, 1678, 1503, 757 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 9.56 (1H, d, J = 2.8 Hz), 8.58-8.55 (2H, m), 8.22-8.01 (10H, m), 7.76 (1H, td, J_1 = 7.7, J_2 = 1.6 Hz), 7.39-7.36 (2H, m), 6.43 (1H, d, J = 5.8 Hz), 5.52 (1H, s), 2.43 (3H, s), 2.40 (3H, s), 1.22 (9H, s); $^{13}C\{^{1}H\}$ NMR (~101 MHz, $CDCl_3$): δ_C 169.5, 163.6, 149.8, 148.3, 141.4, 139.2, 137.1, 136.2, 131.1, 131.0, 130.5, 130.0, 129.3, 129.2, 128.7, 128.2, 127.3, 126.1, 126.1, 125.6, 125.5, 125.0, 124.7, 123.9, 122.1, 55.2, 51.7, 28.5, 20.0, 19.7; HRMS (ESI): *m/z* $[M+H]^+$ calcd for $C_{36}H_{34}N_3O_2$: 540.2651 found, 540.2659.

***N*-(2-(*Tert*-butylamino)-1-(2-(2,3-dihydrobenzo[*b*][1,4]dioxin-6-yl)pyren-1-yl)-2-oxoethyl)picolinamide (6z):** The compound **6z** was obtained after purification by column chromatography on silica gel (EtOAc:hexane = 30:70) as a colourless solid (42 mg, 74%, 0.1 mmol scale); R_f (50% EtOAc/hexane) 0.3; mp: 204-206 ^oC; IR (DCM): 3396, 2977, 1675, 1504, 745 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ_H 9.61 (1H, d, J = 5.6 Hz), 8.59-8.55 (2H, m), 8.21-7.99 (9H, m), 7.74 (1H, td, J_1 = 7.7, J_2 = 1.6 Hz), 7.38-7.35 (1H, m), 7.13-7.09 (2H, m), 6.47 (1H, d, J = 5.8 Hz), 5.52 (1H, s), 4.39 (4H, s), 1.23 (9H, s); $^{13}C\{^1H\}$ NMR (~101 MHz, $CDCl_3$): δ_C 169.5, 163.7, 149.7, 148.3, 143.5, 143.4, 140.7, 137.0, 135.0, 131.1, 131.0, 130.5, 129.4, 129.1, 128.7, 128.3, 127.3, 127.2, 126.1, 126.1, 125.7, 125.6, 125.5, 125.0, 124.7, 123.9, 122.1, 64.5, 55.2, 51.8, 28.5; HRMS (ESI): *m/z* $[M+H]^+$ calcd for $C_{36}H_{32}N_3O_4$: 570.2393 found, 570.2384.



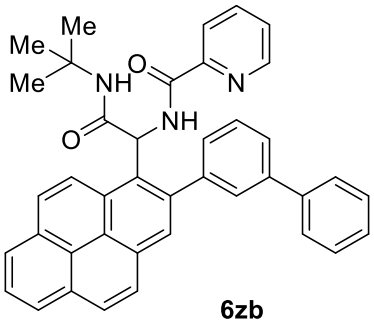
6z

***N*-(2-(*Tert*-butylamino)-1-(2-(1-methyl-1*H*-indol-5-yl)pyren-1-yl)-2-oxoethyl)picolinamide (6za):** The compound **6za** was obtained after purification by column chromatography on silica gel (EtOAc:hexane = 30:70) as a yellow-coloured solid (37 mg, 66%, 0.1 mmol scale); R_f (50% EtOAc/hexane) 0.3; mp: 159-161 ^oC; IR (DCM): 3387, 3015, 1678, 1510, 753 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ_H 9.67-9.66 (1H, m), 8.64 (1H, d, J = 9.2 Hz), 8.58 (1H, d, J = 3.8 Hz), 8.24-8.19 (5H, m), 8.12-8.00 (5H, m), 7.75 (1H, td, J_1 = 7.7, J_2 = 1.6 Hz), 7.58 (1H, br. s), 7.38-7.35 (1H, m), 7.21 (1H, d, J = 3.1 Hz), 6.60-6.52 (2H, m), 5.58 (1H, s), 3.92 (3H, s), 1.21 (9H, s); $^{13}C\{^1H\}$ NMR (~101 MHz, $CDCl_3$): δ_C 169.5, 163.6, 149.8, 148.3, 142.4, 137.0, 136.2, 131.1, 130.8, 130.5, 129.9, 129.9, 129.8, 129.8, 129.7, 129.1, 128.6, 128.5, 128.5, 128.1, 127.9, 127.8, 127.8, 127.3, 126.0, 125.4, 125.3, 124.9, 124.7, 124.1, 122.0, 55.2, 51.6, 33.0, 28.5; HRMS (ESI): *m/z* $[M+H]^+$ calcd for $C_{37}H_{33}N_4O_2$: 565.2604 found, 565.2606.



6za

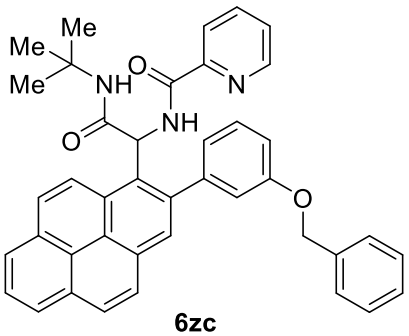
***N*-(1-(2-([1,1'-Biphenyl]-3-yl)pyren-1-yl)-2-(*tert*-butylamino)-2-oxoethyl)picolinamide (6zb):** The compound **6zb** was obtained after purification by column chromatography on silica



6zb

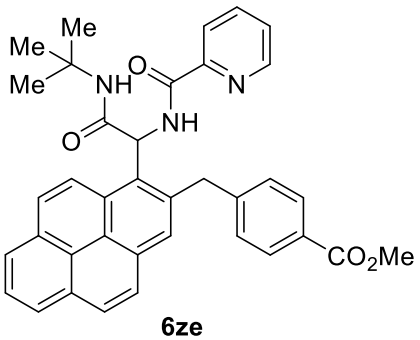
gel (EtOAc:hexane = 30:70) as a brown-coloured semi-solid (31 mg, 53%, 0.1 mmol scale); R_f (50% EtOAc/hexane) 0.1; IR (DCM): 2965, 2921, 1677, 1506, 755 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ_H 9.55-9.54 (1H, m), 8.56-8.51 (2H, m), 8.25-8.20 (5H, m), 8.13 (1H, d, J = 8.9 Hz), 8.08-8.03 (3H, m), 7.79-7.66 (6H, m), 7.46-7.35 (4H, m), 6.47 (1H, d, J = 4.2 Hz), 5.58 (1H, s), 1.20 (9H, s); $^{13}C\{^1H\}$ NMR (~101 MHz, $CDCl_3$): δ_C 169.6, 163.8, 149.7, 148.3, 142.2, 141.3, 140.8, 137.1, 131.2, 131.1, 130.5, 129.3, 129.2, 128.8, 128.8, 128.4, 127.5, 127.5 127.2, 127.2, 126.5, 126.2, 126.1, 125.7, 125.6, 125.1, 124.7, 123.8, 122.1, 55.3, 51.8, 28.5; HRMS (ESI): *m/z* $[M+H]^+$ calcd for $C_{40}H_{34}N_3O_2$: 588.2651 found, 588.2658.

***N*-(1-(2-(3-(Benzyloxy)phenyl)pyren-1-yl)-2-(*tert*-butylamino)-2-oxoethyl)picolinamide (6zc):** The compound **6zc** was obtained after purification by column chromatography on silica gel (EtOAc:hexane = 30:70) as a brown-coloured solid (30 mg, 49%, 0.1 mmol scale); R_f (50% EtOAc/hexane) 0.3; mp: 130-132 ^oC; IR (DCM): 3389, 2964, 1675, 1506, 741 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ_H 9.61 (1H, s), 8.59-8.55 (2H, m), 8.23-8.01 (9H, m), 7.75 (1H, td, J_1 = 7.7, J_2 = 1.5 Hz), 7.54-7.36 (8H, m), 7.18-7.15 (1H, m), 6.44-6.44 (1H, m), 5.52 (1H, br. s), 5.24-5.18 (2H, m), 1.22 (9H, s); $^{13}C\{^1H\}$ NMR (~101 MHz, $CDCl_3$): δ_C 169.4, 163.7, 158.8, 149.7, 148.3, 143.1, 141.0, 137.1, 137.0, 131.1, 131.0, 130.4, 129.7, 129.1, 128.7, 128.5, 128.3, 128.0, 127.8, 127.7, 127.2, 126.9, 126.2, 126.1, 125.6, 125.5, 125.0, 124.6, 123.8, 122.0, 116.6, 70.0, 55.1, 51.7, 28.5; HRMS (ESI): *m/z* $[M+H]^+$ calcd for $C_{41}H_{36}N_3O_3$: 618.2757 found, 618.2756.



6zc

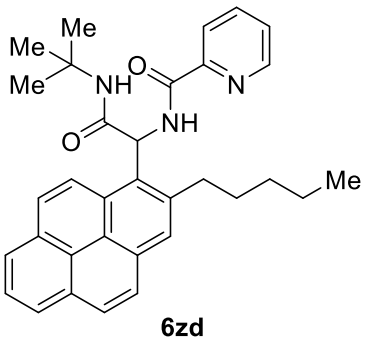
Methyl 4-((1-(2-(*tert*-butylamino)-2-oxo-1-(picolinamido)ethyl)pyren-2-yl)methyl)benzoate (6ze): The compound **6ze** was obtained after purification by column chromatography on silica gel (EtOAc:hexane = 30:70) as a brown-coloured solid (28 mg, 48%, 0.1 mmol scale); R_f (50% EtOAc/hexane) 0.4; mp: 123-125 ^oC; IR (DCM): 3395, 3051, 1711, 1506, 745 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ_H 9.72 (1H, d, J = 4.8 Hz), 8.58 (1H, d, J = 4.3 Hz), 8.34-8.33 (1H, m), 8.25-8.19 (3H, m), 8.16-8.12 (3H,



6ze

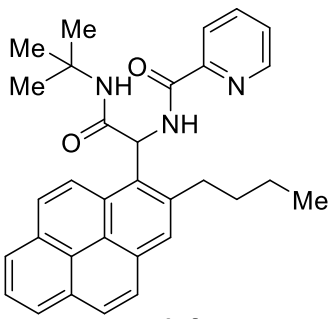
m), 8.09-7.98 (4H, m), 7.76 (1H, td, J_1 = 7.7, J_2 = 1.6 Hz), 7.51 (2H, d, J = 7.5 Hz), 7.39-7.35 (1H, m), 6.43 (1H, d, J = 3.8 Hz), 5.58-5.53 (1H, m), 4.65 (1H, d, J = 15.7 Hz), 4.37-4.33 (1H, m), 3.91 (3H, s), 0.89 (9H, s); $^{13}C\{^1H\}$ NMR (~101 MHz, $CDCl_3$): δ_C 169.7, 166.7, 164.5, 149.6, 148.4, 147.4, 137.1, 131.7, 131.0, 130.5, 130.4, 130.3, 130.0, 129.1, 128.8, 128.4, 128.4, 128.1, 127.0, 126.2, 126.2, 126.2, 125.8, 125.7, 125.0, 124.6, 123.1, 121.9, 53.5, 52.2, 52.2, 51.5, 28.0; HRMS (ESI): *m/z* $[M+H]^+$ calcd for $C_{37}H_{34}N_3O_4$: 584.2549 found, 584.2554.

***N*-(2-(*Tert*-butylamino)-2-oxo-1-(2-pentylpyren-1-yl)ethyl)picolinamide (6zd):** The compound **6zd** was obtained after purification by column chromatography on silica gel (EtOAc:hexane = 30:70) as a brown-coloured semi-solid (17 mg, 34%, 0.1 mmol scale); R_f (50% EtOAc/hexane) 0.4; IR (DCM): 3368, 2958, 1673, 1505, 744 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ_H 9.56 (1H, d, J = 6.4 Hz), 8.57 (1H, d, J = 4.5 Hz), 8.39-8.34 (1H, m), 8.21-8.17 (3H, m), 8.11-7.99 (5H, m), 7.77 (1H, td, J_1 = 7.7, J_2 = 1.6 Hz), 7.40-7.36 (1H, m), 6.60 (1H, m), 5.31 (1H, s), 3.80-3.69 (1H, m), 3.26-3.23 (1H, m), 1.93-1.88 (2H, m), 1.60-1.36 (4H, m), 1.23 (9H, m), 0.94 (3H, t, J = 7.2 Hz); $^{13}C\{^1H\}$ NMR (~101 MHz, $CDCl_3$): δ_C 170.4, 164.4, 149.6, 148.3, 140.9, 137.1, 131.5, 130.9, 130.2, 129.6, 129.2, 128.6, 128.0, 127.1, 127.1, 126.2, 125.9, 125.6, 125.4, 124.7, 124.3, 123.2, 122.1, 53.4, 51.8, 34.9, 32.3, 32.0, 28.4, 22.7, 14.1; HRMS (ESI): *m/z* $[M+Na]^+$ calcd for $C_{33}H_{35}N_3NaO_2$: 528.2627 found, 528.2614.



6zd

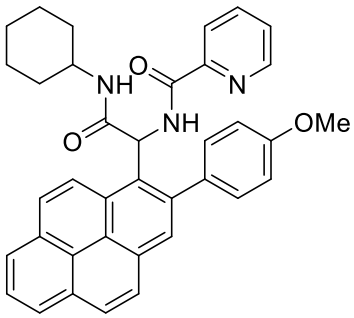
***N*-(2-(*Tert*-butylamino)-1-(2-butylpyren-1-yl)-2-oxoethyl)picolinamide (6zf):** The compound **6zf** was obtained after purification by column chromatography on silica gel (EtOAc:hexane = 30:70) as a brown-coloured semi-solid (18 mg, 37%, 0.1 mmol scale); R_f (50% EtOAc/hexane) 0.4; IR (DCM): 3398, 2954, 1677, 1505, 747 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ_H 9.56 (1H, d, J = 6.5 Hz), 8.57 (1H, d, J = 4.7 Hz), 8.40-8.37 (1H, m), 8.21-8.17 (3H, m), 8.11-8.06 (3H, m), 8.03-7.98 (2H, m), 7.77 (1H, td, J_1 = 7.7, J_2 = 1.7 Hz), 7.39-7.36 (1H, m), 6.62 (1H, s), 5.32 (1H, s), 3.76-3.70 (1H, m), 3.29-3.22 (1H, m), 189-1.87 (2H, m), 1.63-1.58 (2H, m), 1.23 (9H, s), 1.04 (3H, t, J = 7.4 Hz); $^{13}C\{^1H\}$ NMR (~101 MHz, $CDCl_3$): δ_C 170.4, 164.4, 149.6, 148.3, 140.9, 137.1, 131.5, 130.9, 130.2, 129.2, 128.6, 128.0, 127.2, 127.1, 126.2, 125.9, 125.6, 125.4, 124.7, 124.3, 123.2, 122.1, 53.4, 51.8, 34.7,



6zf

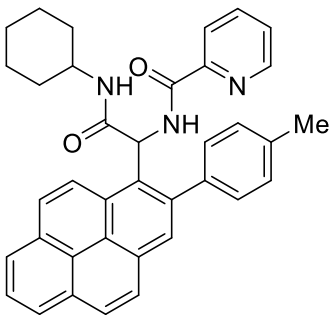
29.7, 28.4, 23.0, 14.2; HRMS (ESI): *m/z* $[M+H]^+$ calcd for $C_{32}H_{34}N_3O_2$: 492.2651 found, 492.2661.

***N*-(2-(Cyclohexylamino)-1-(2-(4-methoxyphenyl)pyren-1-yl)-2-oxoethyl)picolinamide (6zg):** The compound **6zg** was obtained after purification by column chromatography on silica gel (EtOAc:hexane = 30:70) as a brown-coloured solid (42 mg, 74%, 0.1 mmol scale); R_f (50% EtOAc/hexane) 0.3; mp: 128-130 °C; IR (DCM): 1674, 1509, 1252, 836, 503 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ_H 9.38 (1H, d, *J* = 5.8 Hz), 8.42 (1H, d, *J* = 4.4 Hz), 8.38 (1H, d, *J* = 9.3 Hz), 8.08-8.05 (3H, m), 8.02 (1H, s), 7.97-7.86 (5H, m), 7.64-7.60 (3H, m), 7.25-7.22 (1H, m), 7.00 (2H, d, *J* = 8.3 Hz), 6.40 (1H, d, *J* = 6.0 Hz), 5.49 (1H, d, *J* = 8.0 Hz), 3.81 (3H, s), 3.68-3.65 (1H, m), 1.77-1.73 (1H, m), 1.62-1.59 (1H, m), 1.50-1.47 (1H, m), 1.40-1.33 (1H, m), 1.24-1.06 (2H, m), 0.96-0.88 (2H, m), 0.74-0.66 (1H, m); $^{13}C\{^1H\}$ NMR (~101 MHz, $CDCl_3$): δ_C 169.6, 163.8, 159.3, 149.5, 148.2, 141.1, 137.1, 133.9, 131.3, 131.1, 131.0, 130.4, 129.2, 129.2, 128.8, 128.3, 127.4, 127.2, 126.2, 126.1, 125.6, 125.5, 124.9, 124.6, 123.7, 122.1, 114.0, 55.4, 54.9, 48.8, 32.7, 32.5, 25.3, 24.6, 24.4; HRMS (ESI): *m/z* $[M+H]^+$ calcd for $C_{37}H_{34}N_3O_3$: 568.2600 found, 568.2593.



6zg

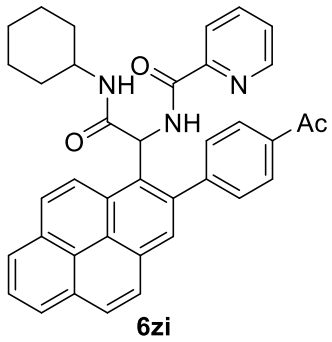
***N*-(2-(Cyclohexylamino)-2-oxo-1-(2-(*p*-tolyl)pyren-1-yl)ethyl)picolinamide (6zh):** The compound **6zh** was obtained after purification by column chromatography on silica gel (EtOAc:hexane = 30:70) as a brown-coloured semi-solid (39 mg, 72%, 0.1 mmol scale); R_f (50% EtOAc/hexane) 0.3; IR (DCM): 2927, 1669, 1502, 736, 513 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ_H 9.48 (1H, d, *J* = 5.6 Hz), 8.56 (1H, d, *J* = 4.0 Hz), 8.50 (1H, d, *J* = 9.2 Hz), 8.23-8.19 (3H, m), 8.15 (1H, s), 8.12-8.01 (5H, m), 7.78-7.75 (2H, m), 7.41-7.39 (3H, m), 6.48 (1H, d, *J* = 5.9 Hz), 5.59 (1H, d, *J* = 8.0 Hz), 3.79-3.77 (1H, m), 2.52 (3H, s), 1.88-1.71 (2H, m), 1.63-1.60 (1H, m), 1.53-1.46 (2H, m), 1.33-1.22 (2H, m), 1.08-0.99 (2H, m), 0.83-0.80 (1H, m); $^{13}C\{^1H\}$ NMR (~101 MHz, $CDCl_3$): δ_C 169.6, 163.8, 149.5, 148.2, 141.5, 138.7, 137.5, 137.3, 131.1, 131.1, 130.4, 129.3, 129.3, 129.2, 129.2, 129.0, 128.8, 128.3, 127.2, 126.2, 126.2, 125.7, 125.6, 124.9,



6zh

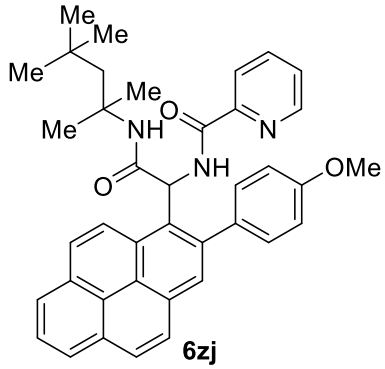
124.7, 123.8, 122.2, 54.9, 48.8, 32.7, 32.5, 25.4, 24.7, 24.5, 21.4; HRMS (ESI): *m/z* $[M+H]^+$ calcd for $C_{37}H_{34}N_3O_2$: 552.2651 found, 552.2656.

***N*-(1-(2-(4-Acetylphenyl)pyren-1-yl)-2-(cyclohexylamino)-2-oxoethyl)picolinamide (6zi):** The compound **6zi** was obtained after purification by column chromatography on silica gel (EtOAc:hexane = 30:70) as a brown-coloured semi-solid (43 mg, 74%, 0.1 mmol scale); R_f (50% EtOAc/hexane) 0.3; IR (DCM): 2930, 2855, 1676, 498 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ_H 9.44 (1H, d, *J* = 6.0 Hz), 8.53 (1H, d, *J* = 4.4 Hz), 8.46 (1H, d, *J* = 9.3 Hz), 8.24-8.11 (8H, m), 8.06-8.03 (3H, m), 7.78-7.75 (2H, m), 7.40-7.37 (1H, m), 6.39 (1H, d, *J* = 6.2 Hz), 5.69 (1H, d, *J* = 7.9 Hz), 3.82-3.78 (1H, m), 2.73 (3H, s), 1.91-1.87 (2H, m), 1.78-1.75 (1H, m), 1.64-1.48 (2H, m), 1.38-1.21 (2H, m), 1.11-1.02 (2H, m), 0.91-0.81 (1H, m);$^{13}C\{^1H\}$ NMR (~101 MHz, $CDCl_3$): δ_C 197.9, 169.4, 163.9, 149.2, 148.2, 146.7, 140.4, 137.3, 136.3, 131.2, 131.1, 130.5, 129.3, 129.2, 128.6, 128.5, 127.1, 126.6, 126.4, 126.4, 126.0, 125.8, 125.2, 124.6, 123.4, 122.3, 54.9, 48.9, 32.7, 32.6, 26.8, 25.3, 24.7, 24.5; HRMS (ESI): *m/z* $[M+H]^+$ calcd for $C_{37}H_{34}N_3O_3$: 580.2600 found, 580.2607.



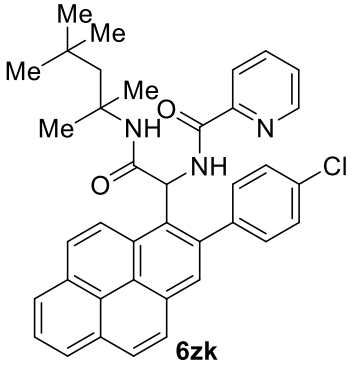
6zi

***N*-(1-(2-(4-Methoxyphenyl)pyren-1-yl)-2-oxo-2-((2,4,4-trimethylpentan-2-yl)amino)ethyl)picolinamide (6zj):** The compound **6zj** was obtained after purification by column chromatography on silica gel (EtOAc:hexane = 30:70) as a brown-coloured solid (53 mg, 90%, 0.1 mmol scale); R_f (50% EtOAc/hexane) 0.3; mp: 178-180 ^oC; IR (DCM): 3379, 2957, 1678, 1502, 1248 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ_H 9.53-9.53 (1H, m), 8.45 (1H, d, *J* = 4.4 Hz), 8.39 (1H, d, *J* = 9.3 Hz), 8.07-8.02 (5H, m), 7.96-7.85 (5H, m), 7.61 (1H, t, *J* = 7.6 Hz), 7.24-7.21 (1H, m), 7.01 (2H, d, *J* = 8.1 Hz), 6.31 (1H, d, *J* = 4.3 Hz), 5.37 (1H, s), 3.81 (3H, s), 1.53 (1H, d, *J* = 14.9 Hz), 1.33 (1H, d, *J* = 14.9 Hz), 1.20 (3H, s), 1.12 (3H, s), 0.50 (9H, s); $^{13}C\{^1H\}$ NMR (~101 MHz, $CDCl_3$): δ_C 169.1, 163.7, 159.3, 149.7, 148.2, 140.9, 137.0, 133.9, 131.5, 131.1, 131.0, 130.4, 129.2, 128.6, 128.2, 127.4, 127.2, 126.1, 125.6, 125.5, 124.9, 124.6, 123.9, 122.0, 114.0, 55.7, 55.4, 52.2, 31.2, 31.0, 29.0, 28.2; HRMS (ESI): *m/z* $[M+H]^+$ calcd for $C_{39}H_{40}N_3O_3$: 598.3070 found, 598.3073.

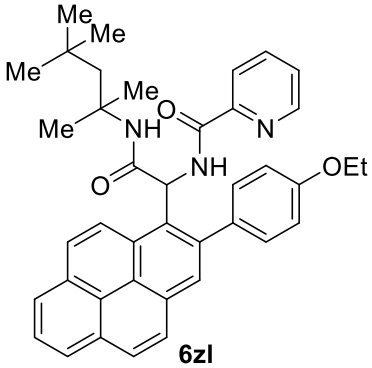


6zj

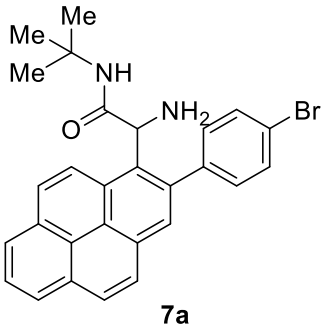
***N*-(1-(2-(4-Chlorophenyl)pyren-1-yl)-2-oxo-2-((2,4,4-trimethylpentan-2-yl)amino)ethyl)picolinamide (6zk):** The compound **6zk** was obtained after purification by column chromatography on silica gel (EtOAc:hexane = 20:80) as a brown-coloured semi-solid (47 mg, 78%, 0.1 mmol scale); R_f (50% EtOAc/hexane) 0.4; IR (DCM): 2938, 1678, 1506, 729 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ_H 9.61 (1H, br. s), 8.59 (1H, d, *J* = 3.8 Hz), 8.48 (1H, d, *J* = 9.3 Hz), 8.23-8.21 (4H, m), 8.12-8.10 (2H, m), 8.06-8.02 (4H, m), 7.76 (1H, t, *J* = 7.6 Hz), 7.57 (2H, m, d, *J* = 7.3 Hz), 7.40-7.37 (1H, m), 6.32 (1H, d, *J* = 4.1 Hz), 5.53 (1H, s), 1.66 (1H, d, *J* = 14.9 Hz), 1.47 (1H, d, *J* = 14.9 Hz), 1.35 (3H, s), 1.27 (3H, s), 0.65 (9H, s); $^{13}C\{^1H\}$ NMR (~101 MHz, $CDCl_3$): δ_C 169.0, 163.8, 149.5, 148.3, 140.1, 140.1, 137.2, 134.1, 131.1, 130.5, 129.3, 129.0, 128.8, 128.7, 128.5, 127.1, 127.0, 126.3, 126.2, 125.8, 125.7, 125.2, 124.6, 123.7, 122.1, 55.8, 55.3, 52.4, 31.3, 31.0, 29.0, 28.2; HRMS (ESI): *m/z* $[M+H]^+$ calcd for $C_{38}H_{37}ClN_3O_2$: 602.2574 found, 602.2552.



***N*-(1-(2-(4-Ethoxyphenyl)pyren-1-yl)-2-oxo-2-((2,4,4-trimethylpentan-2-yl)amino)ethyl)picolinamide (6zl):** The compound **6zl** was obtained after purification by column chromatography on silica gel (EtOAc:hexane = 30:70) as a brown-coloured semi-solid (53 mg, 87%, 0.1 mmol scale); R_f (50% EtOAc/hexane) 0.3; IR (DCM): 2956, 1680, 1505, 1247 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ_H 9.69 (1H, br. s), 8.59 (1H, d, *J* = 4.2 Hz), 8.53 (1H, d, *J* = 9.2 Hz), 8.20-8.16 (5H, m), 8.09-7.98 (5H, m), 7.74 (1H, t, *J* = 7.4 Hz), 7.38-7.35 (1H, m), 7.14 (2H, d, *J* = 8.1 Hz), 6.46 (1H, d, *J* = 3.0 Hz), 5.51 (1H, s), 4.21-4.15 (2H, m), 1.67 (1H, d, *J* = 14.9 Hz), 1.52 (3H, t, *J* = 6.9 Hz), 1.48 (1H, d, *J* = 14.9 Hz), 1.33 (3H, s), 1.26 (3H, s), 0.64 (9H, s); $^{13}C\{^1H\}$ NMR (~101 MHz, $CDCl_3$): δ_C 169.0, 163.6, 158.6, 149.6, 148.2, 141.0, 137.1, 133.6, 131.5, 131.4, 131.0, 131.0, 130.4, 129.2, 128.6, 128.2, 127.4, 127.2, 126.1, 126.0, 125.5, 125.4, 124.9, 124.6, 123.9, 122.0, 114.5, 63.5, 55.6, 55.3, 52.1, 31.2, 31.0, 29.0, 28.2, 14.9; HRMS (ESI): *m/z* $[M+H]^+$ calcd for $C_{40}H_{42}N_3O_3$: 612.3226 found, 612.3203.



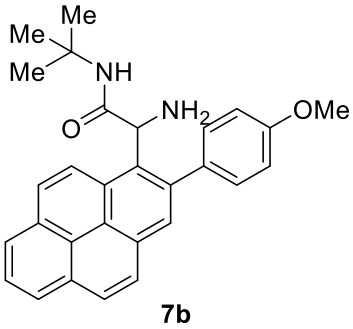
2-Amino-2-(2-(4-bromophenyl)pyren-1-yl)-*N*-(*tert*-butyl)acetamide (7a): The compound **7a** was obtained after purification by column chromatography on silica gel (EtOAc:hexane =



7a

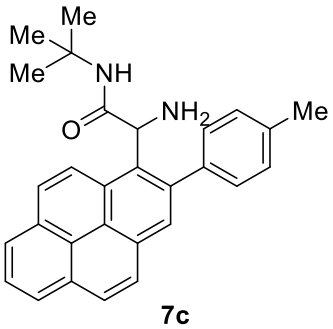
30:70) as a brown-coloured semi-solid (28 mg, 58%, 0.1 mmol scale); R_f (50% EtOAc/hexane) 0.2; IR (DCM): 3324, 2956, 1667, 1507, 760 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ_H 8.28 (1H, d, J = 9.3 Hz), 8.22-8.15 (3H, m), 8.10-8.01 (5H, m), 7.68-7.66 (3H, m), 7.44 (1H, s), 5.04 (1H, s), 2.18 (2H, s), 1.43 (9H, s); $^{13}C\{^1H\}$ NMR (~101 MHz, $CDCl_3$): δ_C 173.4, 141.1, 139.8, 133.9, 131.5, 131.2, 130.5, 128.5, 128.4, 128.1, 127.2, 126.4, 126.2, 125.6, 125.4, 125.3, 124.9, 123.7, 121.9, 56.0, 51.1, 28.7; HRMS (ESI): *m/z* $[M+H]^+$ calcd for $C_{28}H_{26}BrN_2O$: 485.1229 found, 485.1230.

2-Amino-*N*-(*tert*-butyl)-2-(2-(4-methoxyphenyl)pyren-1-yl)acetamide (7b): The compound **7b** was obtained after purification by column chromatography on silica gel (EtOAc:hexane = 30:70) as a brown-coloured semi-solid (40 mg, 93%, 0.1 mmol scale); R_f (50% EtOAc/hexane) 0.2; IR (DCM): 2923, 1678, 1513, 1239, 758 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ_H 8.30 (1H, d, J = 9.3 Hz), 8.20 (2H, dd, J_1 = 7.6, J_2 = 2.7 Hz), 8.15 (1H, d, J = 9.4 Hz), 8.11-8.07 (2H, m), 8.04-8.00 (2H, m), 7.63-7.60 (2H, m), 7.24 (1H, s), 7.09 (2H, d, J = 8.8 Hz), 5.15 (1H, s), 3.93 (3H, s), 1.95 (2H, s), 1.40 (9H, s); $^{13}C\{^1H\}$ NMR (~101 MHz, $CDCl_3$): δ_C 173.7, 159.1, 140.8, 134.5, 134.2, 131.1, 130.5, 130.4, 128.5, 128.2, 127.9, 127.3, 127.0, 126.0, 125.5, 125.3, 125.1, 125.0, 123.9, 113.8, 56.0, 55.4, 51.0, 28.7; HRMS (ESI): *m/z* $[M+Na]^+$ calcd for $C_{29}H_{28}N_2NaO_2$: 459.2048 found, 459.2049.



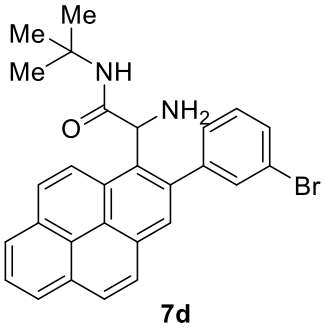
7b

2-Amino-*N*-(*tert*-butyl)-2-(2-(*p*-tolyl)pyren-1-yl)acetamide (7c): The compound **7c** was obtained after purification by column chromatography on silica gel (EtOAc:hexane = 30:70) as a brown-coloured semi-solid (28 mg, 56%, 0.12 mmol scale); R_f (50% EtOAc/hexane) 0.2; IR (DCM): 3369, 2968, 1674, 1512, 1248 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ_H 8.32 (1H, d, J = 9.3 Hz), 8.22-8.15 (3H, m), 8.11-8.00 (4H, m), 7.57-7.57 (2H, m), 7.37 (2H, d, J = 8.0 Hz), 7.19 (1H, s), 5.15 (1H, s), 2.51 (3H, s), 2.12 (2H, s), 1.41 (9H, s); $^{13}C\{^1H\}$ NMR (~101 MHz, $CDCl_3$): δ_C 173.7, 141.2, 139.2, 137.2, 134.0, 131.1, 130.5, 130.5, 129.9, 129.1, 128.5, 128.2, 127.9, 127.3, 126.9, 126.0, 125.5, 125.3, 125.1, 125.0, 124.0, 56.0, 51.0, 28.7, 21.3; HRMS (ESI): *m/z* $[M+H]^+$ calcd for $C_{29}H_{29}N_2O$: 421.2280 found, 421.2273.



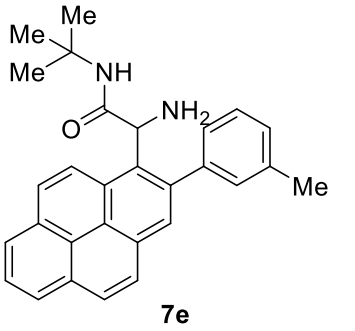
7c

2-Amino-2-(2-(3-bromophenyl)pyren-1-yl)-*N*-(*tert*-butyl)acetamide (7d): The compound **7d** was obtained after purification by column chromatography on silica gel (EtOAc:hexane = 30:70) as a brown-coloured semi-solid (17 mg, 28%, 0.13 mmol scale); R_f (50% EtOAc/hexane) 0.2; mp: 158-160 °C; IR (DCM): 3327, 2970, 1666, 1510, 751 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ_H 8.30 (1H, d, J = 9.3 Hz), 8.22-8.15 (2H, m), 8.11-8.01 (5H, m), 7.80-7.62 (4H, m), 7.41 (1H, t, J = 7.8 Hz), 5.04 (1H, s), 2.08 (2H, s), 1.42 (9H, s); $^{13}C\{^1H\}$ NMR (~101 MHz, $CDCl_3$): δ_C 173.3, 144.2, 139.5, 132.4, 131.1, 130.5, 130.5, 129.9, 128.5, 128.5, 128.5, 128.4, 128.1, 127.1, 126.4, 126.2, 125.6, 125.4, 125.3, 124.8, 123.7, 122.4, 56.0, 51.1, 28.7; HRMS (ESI): *m/z* $[M+H]^+$ calcd for $C_{28}H_{26}BrN_2O$: 485.1229 found, 485.1234.



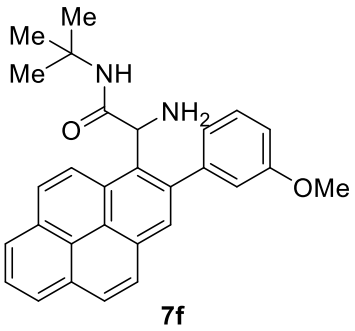
7d

2-Amino-*N*-(*tert*-butyl)-2-(2-(*m*-tolyl)pyren-1-yl)acetamide (7e): The compound **7e** was obtained after purification by column chromatography on silica gel (EtOAc:hexane = 30:70) as a brown-coloured solid (40 mg, 56%, 0.17 mmol scale); R_f (50% EtOAc/hexane) 0.2; mp: 120-122 °C; IR (DCM): 3396, 2923, 1677, 1512, 759 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ_H 8.33 (1H, d, J = 9.3 Hz), 8.22-8.15 (3H, m), 8.12-8.07 (2H, m), 8.04-8.01 (2H, m), 7.51-7.31 (4H, m), 7.12-7.11 (1H, m), 5.15 (1H, s), 2.51 (3H, s), 2.35 (2H, br. s), 1.41 (9H, s); $^{13}C\{^1H\}$ NMR (~101 MHz, $CDCl_3$): δ_C 173.4, 142.1, 141.3, 138.1, 138.1, 133.7, 131.1, 130.5, 130.4, 128.6, 128.5, 128.2, 128.2. 127.9, 127.2, 126.7, 126.0, 125.4, 125.3, 125.1, 124.9, 123.9, 56.0, 51.0, 28.7, 21.6; HRMS (ESI): *m/z* $[M+H]^+$ calcd for $C_{29}H_{29}N_2O$: 421.2280 found, 421.2270.



7e

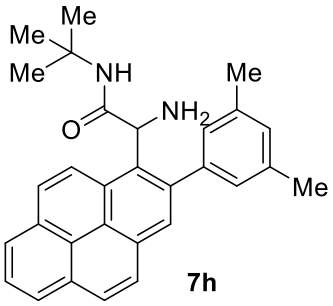
2-Amino-*N*-(*tert*-butyl)-2-(2-(3-methoxyphenyl)pyren-1-yl)acetamide (7f): The compound **7f** was obtained after purification by column chromatography on silica gel (EtOAc:hexane = 30:70) as a brown-coloured solid (25 mg, 45%, 0.13 mmol scale); R_f (50% EtOAc/hexane) 0.2; mp: 95-97 °C; IR (DCM): 2958, 1678, 1513, 1233, 760 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ_H 8.30 (1H, d, J = 9.3 Hz), 8.22-8.13 (4H, m), 8.10-8.01 (3H, m), 7.46 (1H, t, J = 7.8 Hz), 7.28 (3H, br. s), 7.04 (1H, dd, J_1 = 8.3, J_2 = 2.0 Hz), 5.16 (1H, s), 3.91 (3H, s), 2.08 (2H, br. s), 1.41 (9H, s); $^{13}C\{^1H\}$ NMR (~101 MHz, $CDCl_3$): δ_C 173.6, 159.4, 143.5, 141.0, 134.0, 131.2, 130.5, 130.4, 129.5, 129.5, 129.4, 128.5, 128.2, 127.9, 127.3, 126.5,



7f

126.1, 125.5, 125.3, 125.2, 124.9, 123.9, 115.5, 56.1, 55.4, 51.0, 28.7; HRMS (ESI): *m/z* $[M+H]^+$ calcd for $C_{29}H_{29}N_2O_2$: 437.2229 found, 437.2245.

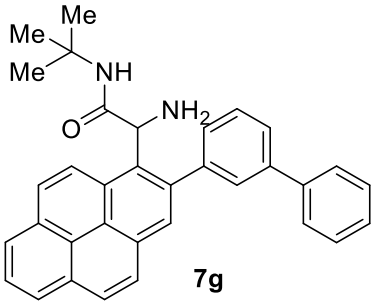
2-Amino-*N*-(*tert*-butyl)-2-(2-(3,5-dimethylphenyl)pyren-1-yl)acetamide (7h): The



7h

compound **7h** was obtained after purification by column chromatography on silica gel (EtOAc:hexane = 30:70) as a brown-coloured semi-solid (16 mg, 62%, 0.06 mmol scale); R_f (50% EtOAc/hexane) 0.2; IR (DCM): 3329, 2964, 1672, 1509, 1227 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ_H 8.31 (1H, d, J = 9.3 Hz), 8.21 (2H, dd, J_1 = 7.6, J_2 = 3.6 Hz), 8.15 (1H, d, J = 9.4 Hz), 8.09 (2H, d, J = 7.8 Hz), 8.05-8.01 (2H, m), 7.28-7.14 (3H, m), 6.97 (1H, s), 5.13 (1H, s), 2.46 (6H, s), 2.05 (2H, br. s), 1.37 (9H, s); $^{13}C\{^1H\}$ NMR (~101 MHz, $CDCl_3$): δ_C 173.5, 142.1, 141.5, 133.7, 131.1, 130.5, 130.4, 129.1, 128.5, 128.2, 127.9, 127.3, 126.7, 126.0, 125.4, 125.3, 125.1, 124.9, 124.1, 56.1, 51.0, 28.7, 21.5; HRMS (ESI): *m/z* $[M-H]^+$ calcd for $C_{30}H_{29}N_2O$: 433.2280 found, 433.2281.

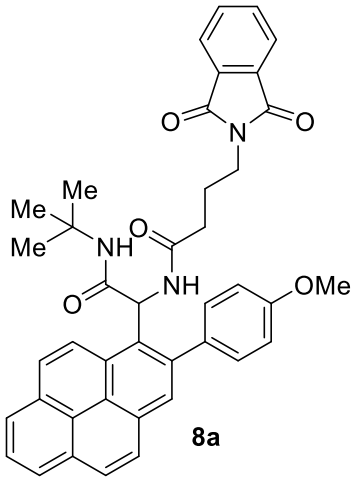
2-(2-([1,1'-Biphenyl]-3-yl)pyren-1-yl)-2-amino-*N*-(*tert*-butyl)acetamide (7g): The



7g

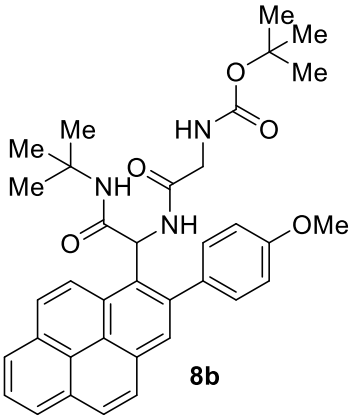
compound **7g** was obtained after purification by column chromatography on silica gel (EtOAc:hexane = 30:70) as a colourless solid (15 mg, 78%, 0.04 mmol scale); R_f (50% EtOAc/hexane) 0.2; mp: 235-237 ^oC; IR (DCM): 2953, 1670, 1510, 839, 762 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ_H 8.32 (1H, d, J = 9.3 Hz), 8.24-8.17 (4H, m), 8.12-8.02 (4H, m), 7.75-7.73 (4H, m), 7.63 (1H, t, J = 7.4 Hz), 7.51-7.47 (2H, m), 7.42-7.38 (2H, m), 5.21 (1H, s), 2.27 (2H, br. s), 1.41 (9H, s); $^{13}C\{^1H\}$ NMR (~101 MHz, $CDCl_3$): δ_C 173.5, 142.6, 141.2, 141.1, 131.2, 130.5, 128.9, 128.7, 128.6, 128.5, 128.3, 128.0, 127.6, 127.6, 127.3, 126.7, 126.2, 126.1, 125.6, 125.4, 125.2, 124.9, 123.9, 56.1, 51.1, 28.7; HRMS (ESI): *m/z* $[M+H]^+$ calcd for $C_{34}H_{31}N_2O$: 483.2436 found, 483.2415.

***N*-(2-(*Tert*-butylamino)-1-(2-(4-methoxyphenyl)pyren-1-yl)-2-oxoethyl)-4-(1,3-dioxoisoindolin-2-yl)butanamide (8a):** The compound **8a** was obtained after purification by column chromatography on silica gel (EtOAc:hexane = 30:70) as a brown-coloured solid (37 mg, 58%, 0.1 mmol scale); R_f (50% EtOAc/hexane) 0.25; mp: 170-172 °C; IR (DCM): 3408, 3018, 1705, 1507, 741 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ_H 8.42 (1H, d, J = 9.4 Hz), 8.22-8.00 (9H, m), 7.74 (2H, dd, J_1 = 5.4, J_2 = 3.0 Hz), 7.62 (2H, dd, J_1 = 5.4, J_2 = 3.0 Hz), 7.28 (1H, br. s), 7.11 (2H, d, J = 8.2 Hz), 6.26 (1H, d, J = 5.6 Hz), 5.52 (1H, s), 3.93 (3H, s), 3.67 (2H, t, J = 6.4 Hz), 2.27-2.23 (2H, m), 2.00-1.90 (2H, m), 1.20 (9H, s); $^{13}C\{^1H\}$ NMR (~101 MHz, $CDCl_3$): δ_C 171.2, 169.7, 168.4, 159.3, 140.9, 133.9, 133.8, 131.9, 131.1, 130.9, 130.4, 129.7, 128.9, 128.5, 128.2, 127.5, 127.2, 126.1, 125.6, 125.5, 124.9, 124.7, 123.8, 123.1, 113.9, 55.4, 55.0, 51.8, 37.2, 33.6, 28.5, 24.8; HRMS (ESI): *m/z* $[M+Na]^+$ calcd for $C_{41}H_{37}N_3NaO_5$: 674.2631 found, 674.2655.



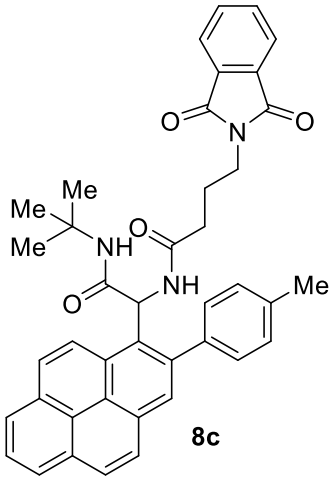
8a

***Tert*-butyl (2-((2-(*tert*-butylamino)-1-(2-(4-methoxyphenyl)pyren-1-yl)-2-oxoethyl)amino)-2-oxoethyl)carbamate (8b):** The compound **8b** was obtained after purification by column chromatography on silica gel (EtOAc:hexane = 30:70) as a brown-coloured solid (12 mg, 42%, 0.05 mmol scale); R_f (50% EtOAc/hexane) 0.2; mp: 213-215 °C; IR (DCM): 3357, 2965, 1680, 1512, 752 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ_H 8.30 (1H, d, J = 9.4 Hz), 8.23 (2H, dd, J_1 = 7.5, J_2 = 1.4 Hz), 8.17-8.02 (6H, m), 7.50 (2H, broad signal), 7.10 (2H, d, J = 8.3 Hz), 6.24 (1H, d, J = 3.9 Hz), 5.56 (1H, s), 5.06 (1H, br. s), 3.94 (3H, s), 3.77 (2H, d, J = 3.8 Hz), 1.42 (9H, s), 1.21 (9H, s); $^{13}C\{^1H\}$ NMR (~101 MHz, $CDCl_3$): δ_C 169.4, 168.4, 159.3, 141.0, 133.8, 131.1, 131.0, 130.4, 129.2, 128.9, 128.8, 128.3, 127.4, 127.2, 126.2, 125.8, 125.6, 124.9, 124.7, 123.2, 114.0, 80.2, 55.4, 54.8, 51.8, 44.2, 29.7, 28.4, 28.2; HRMS (ESI): *m/z* $[M+H]^+$ calcd for $C_{36}H_{40}N_3O_5$: 594.2968 found, 594.2968.



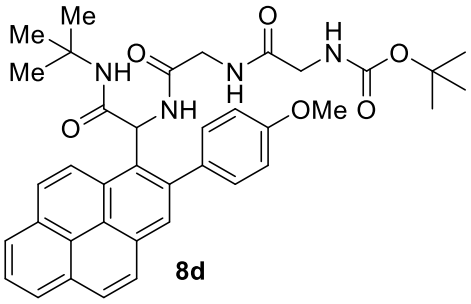
8b

***N*-(2-(*T*ert-butylamino)-2-oxo-1-(2-(*p*-tolyl)pyren-1-yl)ethyl)-4-(1,3-dioxoisoindolin-2-yl)butanamide (8c):** The compound **8c** was obtained after purification by column chromatography on silica gel (EtOAc:hexane = 30:70) as a brown-coloured semi-solid (43 mg, 68%, 0.1 mmol scale); R_f (50% EtOAc/hexane) 0.25; IR (DCM): 3406, 3020, 1706, 1508, 742 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ_H 8.43 (1H, d, J = 9.4 Hz), 8.23-8.01 (8H, m), 7.76-7.74 (2H, m), 7.64-7.62 (2H, m), 7.38 (2H, d, J = 7.0 Hz), 7.25-7.24 (1H, m), 6.23 (1H, d, J = 5.6 Hz), 5.51 (1H, s), 3.68 (2H, t, J = 6.6 Hz), 2.50 (3H, s), 2.26-2.22 (2H, m), 2.00-1.88 (2H, m), 1.20 (9H, s) (one proton count is less); $^{13}C\{^1H\}$ NMR (~101 MHz, $CDCl_3$): δ_C 171.1, 169.7, 168.4, 141.3, 138.7, 137.5, 133.8, 131.9, 131.1, 130.9, 130.4, 129.6, 129.2, 129.2, 128.9, 128.6, 128.2, 127.3, 127.2, 126.2, 125.6, 125.5, 125.0, 124.7, 123.8, 123.2, 55.1, 51.8, 37.2, 33.6, 28.5, 24.8, 21.4; HRMS (ESI): *m/z* $[M+H]^+$ calcd for $C_{41}H_{38}N_3O_4$: 636.2862 found, 636.2870.



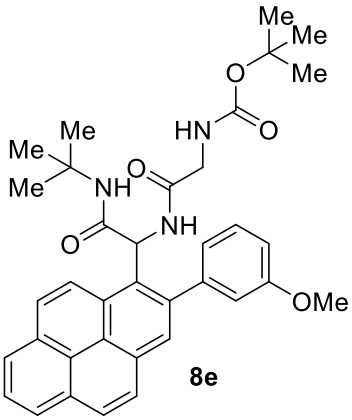
8c

***Tert*-butyl (2-((2-((2-(*tert*-butylamino)-1-(2-(4-methoxyphenyl)pyren-1-yl)-2-oxoethyl)amino)-2-oxoethyl)amino)-2-oxoethyl)carbamate (8d):** The compound **8d** was obtained after purification by column chromatography on silica gel (EtOAc:hexane = 90:10) as a colourless semi-solid (26 mg, 40%, 0.1 mmol scale); R_f (60% EtOAc/hexane) 0.1; IR (DCM): 3346, 2858, 1675, 1508, 756 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ_H 8.28 (1H, d, J = 9.3 Hz), 8.21 (2H, d, J = 7.6 Hz), 8.17-8.00 (6H, m), 7.56 (2H, broad signal), 7.08 (2H, d, J = 8.4 Hz), 6.81 (1H, br. s), 6.20-6.19 (1H, m), 5.38 (1H, s), 5.22 (1H, t, J = 5.6 Hz), 3.91 (3H, s), 4.00-3.81 (2H, m), 3.74 (2H, br. s), 1.38 (9H, s), 1.16 (9H, s); $^{13}C\{^1H\}$ NMR (~101 MHz, $CDCl_3$): δ_C 169.9, 169.2, 167.7, 159.3, 155.9, 141.0, 133.7, 131.1, 131.1, 130.4, 128.9, 128.8, 128.8, 128.4, 127.4, 127.2. 126.3, 125.8, 125.7, 124.9, 124.6, 123.3, 113.8, 80.1, 55.4, 55.1, 51.9, 43.9, 42.7, 28.4, 28.2; HRMS (ESI): *m/z* $[M+Na]^+$ calcd for $C_{38}H_{42}N_4NaO_6$: 673.3002 found, 673.3001.



8d

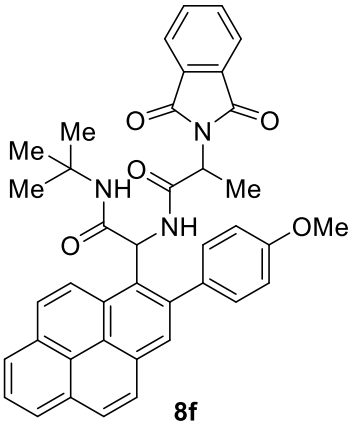
***Tert*-butyl (2-((2-(*tert*-butylamino)-1-(2-(3-methoxyphenyl)pyren-1-yl)-2-oxoethyl)amino)-2-oxoethyl)carbamate (8e):** The compound **8e** was obtained after



8e

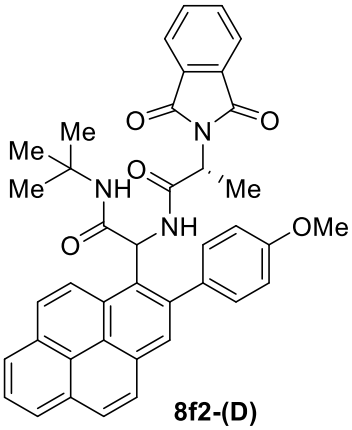
purification by column chromatography on silica gel (EtOAc:hexane = 30:70) as a brown-coloured solid (8 mg, 30%, 0.048 mmol scale); R_f (50% EtOAc/hexane) 0.2; mp: 225-227 ^oC; IR (DCM): 3384, 2931, 1711 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ_H 8.33 (1H, d, J = 8.9 Hz), 8.24-8.22 (2H, m), 8.17 (1H, d, J = 9.4 Hz), 8.13-8.11 (2H, m), 8.07-8.03 (2H, m), 7.48-7.47 (3H, m), 7.07-7.05 (2H, m), 6.22 (1H, br. s), 5.65-5.51 (1H, m), 5.05 (1H, s), 3.91 (3H, s), 3.77 (2H, s), 1.42 (9H, s), 1.20 (9H, s); $^{13}C\{^1H\}$ NMR (~101 MHz, $CDCl_3$): δ_C 169.2, 168.3, 159.5, 155.9, 143.0, 141.0, 131.1, 131.0, 130.4, 129.5, 128.9, 128.8, 128.8, 128.4, 127.2, 126.9, 126.3, 125.8, 125.6, 125.1, 124.7, 123.3, 115.8, 80.1, 55.4, 54.8, 51.8, 44.2, 28.4, 28.2; HRMS (ESI): *m/z* $[M+Na]^+$ calcd for $C_{36}H_{39}N_3NaO_5$: 616.2787 found, 616.2782.

***N*-(2-(*Tert*-butylamino)-1-(2-(4-methoxyphenyl)pyren-1-yl)-2-oxoethyl)-2-(1,3-dioxoisoindolin-2-yl)propanamide (8f):** The compound **8f** was obtained after purification by column chromatography on silica gel (EtOAc:hexane = 30:70) as a brown-coloured semi-solid (40 mg, 70% (diastereomers, 70:30), 0.09 mmol scale); R_f (50% EtOAc/hexane) 0.2; IR (DCM): 3400, 2942, 1711, 1512, 762 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ_H 8.38-7.93 (8H, m), 7.87-7.85 (2H, m), 7.78-7.75 (2H, m), 7.72-7.64 (2H, m), 7.53 (1H, broad signal), 7.10-7.00 (2H, m), 6.32 (1H, br. s), 5.63 (1H, br. s), 4.89-4.84 (1H, m), 3.93 (3H, s), 1.59 (3H, d, J = 7.2 Hz), 1.22 (9H, s) (the compound exists as diastereomers and approximate signals corresponding to major isomer are represented); $^{13}C\{^1H\}$ NMR (~101 MHz, $CDCl_3$): δ_C 169.4, 169.3, 168.2, 167.9, 167.6, 167.4, 159.3, 159.1, 134.3, 134.0, 133.9, 133.9, 131.8, 131.2, 131.1, 130.9, 130.9, 130.4, 130.3, 129.4, 129.3, 128.6, 128.5, 128.2, 127.7, 127.6, 127.3, 127.2, 126.1, 125.7, 125.6, 125.5, 125.4, 124.9, 124.7, 124.6, 123.6, 123.4, 123.3, 123.2, 114.0, 55.4, 55.4, 55.3, 55.3, 51.9, 51.8, 49.3, 48.9, 28.5, 28.5, 15.3, 15.0 (the compound exists as diastereomers and all signals corresponding to both isomers are represented); HRMS (ESI): *m/z* $[M+H]^+$ calcd for $C_{40}H_{36}N_3O_5$: 638.2655 found, 638.2656.



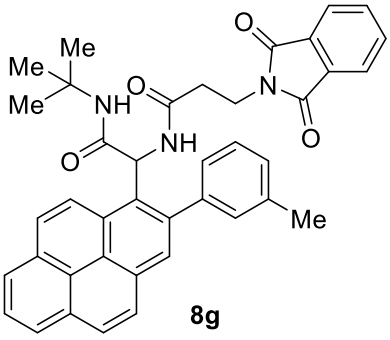
8f

(*2R*)-*N*-(2-(*Tert*-butylamino)-1-(2-(4-methoxyphenyl)pyren-1-yl)-2-oxoethyl)-2-(1,3-dioxoisoindolin-2-yl)propanamide (8f2-(D)): The compound **8f2-(D)** was obtained after purification by column chromatography on silica gel (EtOAc:hexane = 30:70) as a brown- coloured semi-solid (20 mg, 62%(diastereomers, 69:31), 0.05 mmol scale); R_f (50% EtOAc/hexane) 0.2; IR (DCM): 3395, 2954, 1703, 1506, 747 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ_H 8.38-7.93 (8H, m), 7.87-7.84 (2H, m), 7.77-7.75 (2H, m), 7.73-7.64 (2H, m), 7.51 (1H, broad signal), 7.10 (1H, broad signal), 6.99 (1H, broad signal), 6.31 (1H, br. s), 5.63 (1H, br. s), 4.89-4.81 (1H, m), 3.93 (3H, s), 1.59 (3H, d, J = 7.2 Hz), 1.22 (9H, s) (the compound exists as rotamers and approximate signals corresponding to major isomer are represented); $^{13}C\{^1H\}$ NMR (~101 MHz, $CDCl_3$): δ_C 169.4, 169.3, 168.2, 167.9, 167.6, 167.4, 159.3, 159.1, 134.3, 134.0, 133.9, 133.9, 131.8, 131.2, 131.2, 131.1, 130.9, 130.9, 130.4, 130.3, 129.4, 129.3, 128.6, 128.6, 128.5, 128.5, 128.4, 128.2, 127.7, 127.6, 127.3, 127.2, 126.1, 125.7, 125.6, 125.4, 125.4, 124.9, 124.7, 124.6, 123.6, 123.4, 123.3, 123.2, 114.0, 55.4, 55.4, 55.3, 55.3, 51.9, 51.8, 49.3, 48.9, 28.5, 28.5, 15.3, 15.0; HRMS (ESI): *m/z* $[M+H]^+$ calcd for $C_{40}H_{36}N_3O_5$: 638.2655 found, 638.2658.



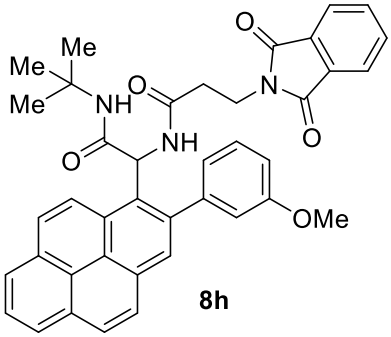
8f2-(D)

***N*-(2-(*Tert*-butylamino)-2-oxo-1-(2-(*m*-tolyl)pyren-1-yl)ethyl)-3-(1,3-dioxoisoindolin-2-yl)propanamide (8g):** The compound **8g** was obtained after purification by column chromatography on silica gel (EtOAc:hexane = 30:70) as a brown-coloured semi-solid (18 mg, 42%, 0.07 mmol scale); R_f (50% EtOAc/hexane) 0.25; IR (DCM): 3350, 2964, 1711, 1670, 1507 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ_H 8.27-8.17 (3H, m), 8.11-7.99 (5H, m), 7.51-7.45 (4H, m), 7.34-7.31 (3H, m), 7.17 (2H, broad signal), 6.20-6.19 (1H, m), 5.37 (1H, s), 3.98-3.90 (1H, m), 3.85-3.80 (1H, m), 2.68-2.60 (2H, m), 2.50 (3H, s), 1.15 (9H, s); $^{13}C\{^1H\}$ NMR (~101 MHz, $CDCl_3$): δ_C 169.4, 168.9, 167.8, 141.5, 141.2, 133.4, 131.5, 131.1, 130.8, 130.3, 129.2, 128.6, 128.6, 128.2, 127.2, 127.1, 126.2, 125.6, 125.6, 124.8, 124.6, 123.3, 122.7, 54.8, 51.7, 34.8, 34.4, 28.4, 21.6; HRMS (ESI): *m/z* $[M+Na]^+$ calcd for $C_{40}H_{35}N_3NaO_4$: 644.2525 found, 644.2527.



8g

***N*-(2-(*Tert*-butylamino)-1-(2-(3-methoxyphenyl)pyren-1-yl)-2-oxoethyl)-3-(1,3-dioxoisoindolin-2-yl)propanamide (8h):** The compound **8h** was obtained after purification by column chromatography on silica gel (EtOAc:hexane = 30:70) as a brown-coloured semi-solid (16 mg, 84%, 0.03 mmol scale); R_f (50% EtOAc/hexane) 0.25; IR (DCM): 3396, 2925, 1710, 1670, 720 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ_H 8.27-8.18 (3H, m), 8.12-8.00 (5H, m), 7.70-7.45 (4H. m), 7.31-7.26 (2H, m), 7.16-6.91 (3H, m), 6.20 (1H, d, J = 5.8 Hz), 5.37 (1H, broad signal), 3.94 (3H, s), 3.93-3.79 (2H, m), 2.69-2.61 (2H, m), 1.14 (9H, s); $^{13}C\{^1H\}$ NMR (~101 MHz, $CDCl_3$): δ_C 169.3, 168.9, 167.8, 143.0, 140.9, 133.3, 131.5, 131.2, 130.8, 130.4, 129.2, 128.6, 128.6, 128.2, 127.2, 126.9, 126.2, 125.6, 125.6, 124.9, 124.6, 123.3, 122.7, 115.6, 55.5, 54.8, 51.8, 34.8, 34.4, 28.4; HRMS (ESI): *m/z* $[M+Na]^+$ calcd for $C_{40}H_{35}N_3NaO_5$: 660.2474 found, 660.2489.



8h

References

1. (a) Feng, X.; Hu, J.-Y.; Redshaw, C.; Yamato, T. *Chem. Eur. J.* **2016**, *22*, 11898; (b) Zych, D. *Molecules* **2019**, *24*, 2551; (c) Gong, Y.; Zhan, X.; Li, Q.; Li, Z.; *Sci. China Chem.* **2016**, ***59***, 1623; (d) Casas-Solvas, J. M.; Howgego, J. D.; Davis, A. P.; *Org. Biomol. Chem.* **2014**, ***12***, 212.

2. (a) Karuppannan, S.; Chambron, J.-C.; *Chem. Asian J.* **2011**, *6*, 964; (b) Østergaard, M. E.; Hrdlicka, P. J.; *Chem. Soc. Rev.* **2011**, ***40***, 5771; (c) Figueira-Duarte, T. M.; Müllen, K. *Chem Rev.* **2011**, *111*, 7260; (d) Kowser, Z.; Rayhan, U.; Akther, T.; Redshaw, C.; Yamato, T. *Mater. Chem. Front.* **2021**, *512*, 2173.

3. (a) Young, T. S.; Schultz, P. G. *J. Biol. Chem.* **2010**, *285*, 11039; (b) Hughes, A. B. Ed., Amino Acids, Peptides and Proteins in Organic Chemistry: Volumes 1-5, WILEY-VCH, **2009**; (c) Stevenazzi, A.; Marchini, M.; Sandrone, G.; Vergani, B.; Lattanzio, M. *Bioorg. Med. Chem. Lett.* **2014**, *24*, 5349; (d) Smolskaya, S.; Andreev, Y. A.; *Biomolecules* **2019**, *9*, 255; (e) Strømgaard, A.; Jensen, A. A.; Strømgaard, K. *ChemBioChem* **2004**, *5*, 909; (f) Pollegioni, L.; Servi, S. Eds., Unnatural Amino Acids, Methods and Protocols, Springer Science+Business Media, LLC **2012**.

4. (a) Hendrickson, T. L.; De Crécy-Lagard, V. V.; Schimmel, P. *Annu. Rev. Biochem.* **2004**, *73*, 147; (b) Drienovská, I.; Roelfes, G. *Nat. Catal.* **2020**, *3*, 193; (c) L. Davis and J. W. Chen, *Nat. Rev. Mol. Cell Biol.* **2012**, *13*, 168; (d) Y. Xiong, C. Shi, Li, L.; Tang, Y.;

Zhang, X.; Liao, S.; Zhang, B.; Sun, C.; Ren, C. *New J. Chem.* **2021**, *45*, 15180; (e) Krueger, A. T.; Imperiali, B. *ChemBioChem* **2013**, *14*, 788.

5. (a) Shellaiah, M.; Sun, K.-W. *Biosensors* **2022**, *12*, 550; (b) Stadler, J. M.; Stafforst, T. *Org. Biomol. Chem.* **2014**, *12*, 5260; (c) Luo, Q.; Fan, C.; Ying, W.; Peng, X.; Hu, Y.; Luan, Z.; Ye, S.; Gong, C.; Huang, Y.; Xiao, Y.; Chen, Y.; Xing, M.; Wang, L.; Yang, S. *Adv. Sci.* **2023**, *10*, 2203918; (d) You, L.; Gokel, G. W. *Chem. Eur. J.* **2008**, *14*, 5861; (e) Lister, G. A.; Eccles, N.; Pike, S. J.; Brown, R. A.; Whitehead, G. F. S.; Raftery, J.; Webb, S. J.; Clayden, J. *Chem. Sci.* **2018**, *9*, 6860.

6. (a) Casier, R.; Duhamel, J. *Langmuir* **2022**, *38*, 3623; (b) Guler, M. O.; Claussen, R. C.; Stupp, S. I. *J. Mater. Chem.***2005**, *15*, 4507; (c) Sato, D.; Kondo, T.; Kato, T.; *Bioorg. Med. Chem.* **2018**, *26*, 3468; (d) Maity, D.; Assaf, K. I.; Sicking, W.; Hirchhäuser, C.; Nau, W. M.; Schmuck, C. *Chem. Eur. J.* **2019**, *25*, 13088; (e) Teng, M.-J.; Jia, X.-R.; Yang, S.; Chen, X.-F. Wei, Y. *Adv. Mater.* **2012**, *24*, 1255.

7. (a) Suhartono, M.; Weidlich, M.; Stein, T.; Karas, M.; Dürner, G.; Göbel, M. W. *Eur. J. Org. Chem.* **2008**, 1608; (b) Pereira, G.; Castanheira, E. M. S.; Schellenberg, P.; Belsley, M.; Ferreira, P. M.T.; Monteiro, L. S. *Tetrahedron* **2013**, *69*, 10254; (c) Abreu, A. S.; Catanheira, E. M. S.; Ferreira, P. M. T.; Monteiro, L. S.; Pereira, G. Queiroz, M.-J. R. P. *Eur. J. Org. Chem.* **2008**, 5697.

8. (a) Chen, S.; Wang, L.; Fahmi, N. E.; Benkovic, S. J.; Hecht, S. M. *J. Am. Chem. Soc.* **2012**, *134*, 18883; (b) Sisido, M.; Tanaka, R.; Inai, Y.; Imanishi, Y. *J. Am. Chem. Soc.* **1989**, *111*, 6790; (c) Goedeweeck, R.; Der Auweraer, M. V.; Schryver, F. C. D. *J. Am. Chem. Soc.***1985**, *107*, 2335; (d) Szymańska, A.; Wiczk, W.; Lankiewicz, L. *Amino Acids* **2001**, *21*, 265; (e) Alves, I.; Cowell, S.; Lee, Y. S.; Tang, X.; Davis, P.; Porreca, F.; Hruby, V. J. *Biochem. Biophys. Res. Commun.* **2004**, *318*, 335; (f) Mihara, H.; Nishino, N.; Fujimoto, T. *Chem. Lett.* **1992**, 1809; (g) Nishikawa, T.; Tajima, N.; Kitamatsu, M.; Fujiki, M.; Imail, Y. *Org. Biomol. Chem.* **2015**, *13*, 11426; (h) Buranaprapuk, A.; Kumar, C. V.; Jockusch, S.; Turro, N. J. *Tetrahedron* **2000**, *56*, 7019; (i) Hossain, M. A.; Hamasaki, K.; Takahashi, K.; Mihara, H.; Ueno, A. *J. Am. Chem. Soc.* **2001**, *123*, 7435; (j) López-Arbeloa, F.; Goedeweeck, R.; Uttens, F. R.; Schryver, F. C. D.; Sisido, M. *J. Am. Chem. Soc.* **1987**, *109*, 3068; (k) Sasaki, H.; Sisido, M.; Imanishi, Y. *Langmuir* **1990**, *6*, 1008.

9. Batalha, Í. L.; Roque, A. C. A. *J. Chromatogr. B* **2016**, *1031*, 86.

10. For selected reviews on C-H functionalization, see: (a) Kakiuchi, F.; Murai, S. *Acc. Chem. Res.* **2002**, *35*, 826; (b) Chen, X.; Engle, K. M.; Wang, D.-H.; Yu, J.-Q. *Angew.*

Chem. Int. Ed. **2009**, *48*, 5094; (c) Arockiam, P. B.; Bruneau, C.; Dixneuf, P.H.; *Chem. Rev.* **2012**, 112, 5879; (d) Wencel-Delord, J.; Glorius, F. *Nat. Chem.* **2013**, *5*, 369; (e) Girard, S. A.; Knauber, T.; Li, C.-J. *Angew. Chem. Int. Ed.* **2014**, *53*, 74; (f) Kakiuchi, F.; Chatani, N. *Adv. Synth. Catal.* **2003**, *345*, 1077; (g) Yang, Y.; Lan, J.; You, J. *Chem. Rev.* **2017**, *117*, 8787; (h) Shang, R.; Ilies, L.; Nakamura, E. *Chem. Rev.* **2017**, *117*, 9086; (i) Segawa, Y.; Maekawa, T.; Itami, K. *Angew. Chem. Int. Ed.* **2015**, *54*, 66; (j) Sinha, S. K.; Guin, S.; Maiti, S.; Porey, S.; Maiti, D. *Chem. Rev.* **2022**, *122*, 5682; (k) Roger, J.; Gottumukkala, A. L.; Doucet, H. *ChemCatChem* **2010**, *2*, 20; (l) He, J.; Wasa, M.; Chan, K. S. L.; Shao, Q.; Yu, J.-Y. *Chem. Rev.* **2017**, *117*, 8754; (m) Manoharan, R.; Jeganmohan, M. *Asian J. Org. Chem.* **2019**, *8*, 1949; (n) Mingo, M. M.; Rodríguez, N.; Arrayás, R. G.; Carretero, J. C. *Chem. Commun.* **2022**, *58*, 2034; (o) Babu, S. A.; Padmavathi, R.; Suwasia, S.; Dalal, A.; Bhattacharya, D.; Singh, P.; Tomar, R. *Stud. Nat. Prod. Chem.* **2021**, *71*, 311; (p) Besset, T.; Poisson, T.; Pannecoucke, X. *Chem. Eur. J.* **2014**, *20*, 16830; (q) Yanagi, T.; Nogi, K.; Yorimitsu, H. *Tetrahedron Lett.* **2018**, *59*, 2951; (r) Lyons, T. W.; Sanford, M. S. *Chem. Rev.* **2010**, *110*, 1147; (s) Mandal, A.; Dana, S.; Choudhury, D.; Baidya, M. *Chem. Asian J.* **2019**, *14*, 4074; (t) Ackermann, L. *Chem. Rev.* **2011**, *111*, 1315; (u) Miura, M.; Satoh, T.; Hirano, K. *Bull. Chem. Soc. Jpn.* **2014**, *87*, 751; (v) Lu, M.-Z.; Goh, J.; Maraswami, M.; Jia, Z.; Tian, J.-S.; Loh, T.-P. *Chem. Rev.* **2022**, *122*, 17479.

11. For selected reviews on bidentate directing group-aided C-H functionalization, see: (a) Rej, S.; Ano, Y.; Chatani, N. *Chem. Rev.* **2020**, *120*, 1788; (b) Daugulis, O.; Roane, J.; Tran, L. D. *Acc. Chem. Res.* **2015**, *48*, 1053; (c) Sambiagio, C.; Schönbauer, D.; Blieck, R.; Dao-Huy, T.; Pototschnig, G; Schaaf, P.; Wiesinger, T.; Zia, M. F.; Wencel-Delord, J.; Besset, T.; Maes, B. U. W.; Schnürch, M. *Chem. Soc. Rev.* **2018**, *47*, 6603; (d) Liu, B.; Romine, A. M.; Rubel, C. Z.; Engle, K. M.; Shi, B.-F. *Chem. Rev.* **2021**, *121*, 14957; (e) Rit, R. K.; Yadav, M. R.; Ghosh, K.; Sahoo, A. K. *Tetrahedron* **2015**, *71*, 4450; (f) Babu, S. A.; Aggarwal, Y.; Patel, P.; Tomar, R. *Chem. Commun.* **2022**, *58*, 2612; (g) Yang, X.; Shan, G.; Wang, L.; Rao, Y. *Tetrahedron Lett.* **2016**, *57*, 819; (h) Ni, S.-F.; Huang, G.; Chen, Y.; Wright, J. S.; Li, M.; Dang, L. *Coord. Chem. Rev.* **2022**, *455*, 214255.

12. For selected reviews on bidentate directing group-aided C-H functionalization of amino acid derivatives, see: (a) Ackermann, L.; Vicente, R.; Kapdi, A. R. *Angew. Chem. Int. Ed.*, **2009**, *48*, 9792; (b) He, G.; Wang, B.; Nack, W. A.; Chen, G. *Acc. Chem. Res.*, **2016**, *49*, 635; (c) Zhan, B.-B.; Jiang, M.-X.; Shi, B.-F. *Chem. Commun.* **2020**, *56*,

13950; (d) Noisier, A. F. M.; Brimble, M. A. *Chem. Rev*. **2014**, *114*, 8775; (e) Brandhofer, T.; Mancheño, O. G. *Eur. J. Org. Chem*. **2018**, 6050; (f) Correa, A.; *Eur. J. Inorg. Chem.* **2021**, 2928; (g) Jeon, J.; Lee, C.; Park, I.; Hong, S. *Chem. Rec.* **2021**, *21*, 3613.

13. For selected papers on bidentate directing group-aided C-H functionalization, see: (a) Shabashov, D.; Daugulis, O. *J. Am. Chem. Soc.* **2010**, *132*, 3965; (b) Kanyiva, K. S.; Kuninobu, Y.; Kanai, M. *Org. Lett.* **2014**, *16*, 1968; (c) Seki, A.; Takahashi, Y.; *Tetrahedron Lett.* **2021**, *74*, 153130; (d) Xu, J.; Qiao, L.; Shen, J.; Chai, K.; Shen, C.; Zhang, P. *Org. Lett.* **2017**, *19*, 20, 5661; (e) Rej, S.; Chatani, N. *ACS Catal.* **2018**, *8*, 6699; (f) Gutekunst, W. R.; Baran, P. S. *J. Org. Chem.* **2014**, *79*, 2430; (g) Parella, R.; Babu, S. A.; *J. Org. Chem.* **2017**, *82*, 6550; (h) Yu, X.; Yang, F.; Wu, Y.; Wu, Y. *Org. Lett.* **2019**, *21*, 1726; (i) Biswas, S.; Bheemireddy, N. R.; Bal, M.; Steijvoort, B. F. V. Maes, B. U. W. *J. Org. Chem.* **2019**, *84*, 13112; (j) Padmavathi, R.; Babu, S. A. *Org. Biomol. Chem.* **2023**, *21*, 2689; (k) Suwasia, S.; Venkataramani, S.; Babu, S. A. *Org. Biomol. Chem.* **2023**, *21*, 1793; (l) Ghouilem, J.; Tran, C.; Grimblat, N.; Retailleau, P.; Alami, M.; Gandon, V.; Messaoudi, S. *ACS Catal.* **2021**, *11*, 1818; (m) Reddy, C.; Bisht, N.; Parella, R.; Babu, S. A. *J. Org. Chem.* **2016**, *81*, 12143; (n) Padmavathi, R.; Sankar, R.; Gopalakrishnan, B.; Parella, R.; Babu, S. A. *Eur. J. Org. Chem.* **2015**, 3727; (o) Han, J.; Liu, P.; Wang, C.; Wang, Q.; Zhang, J.; Zhao, Y.; Shi, D.; Huang, Z.; Zhao, Y. *Org. Lett.* **2014**, *16*, 5682; (p) Zhang, S.-K.; Yang, X.-Y.; Zhao, X.-M.; Li, P.-X.; Niu, J.-L.; Song, M.-P. *Organometallics* **2015**, *34*, 4331; (q) Huang, L.; Sun, X.; Li, Q.; Qi, C. *J. Org. Chem.* **2014**, *79*, 6720.

14. For selected papers dealing with picolinamide directing group-aided ortho or γ-C(sp^2)-H bonds of aromatic (benzylamine type compounds), see: (a) Nadres, E. T.; Santos, G. I. F.; Shabashov, D.; Daugulis, O. *J. Org. Chem.* **2013**, *78*, 9689; (b) Zhao, Y.; He, G.; Nack, W. A.; Chen, G. *Org. Lett.* **2012**, *14*, 2948; (c) Bolsakova, J.; Lukasevics, L.; Grigorjeva, L. *J. Org. Chem.* **2020**, *85*, 4482; (d) Kuai, C.; Wang, L.; Li, B.; Yang, Z.; Cui, X. *Org. Lett.* **2017**, *19*, 2102; (e) Aggarwal, Y.; Padmavathi, R.; Singh, P.; Babu, S. A. *Asian J. Org. Chem.* **2022**, *11*, e202200327; (f) Bisht, N.; Singh, P.; Babu, S. A. *Synthesis* **2022**, *54*, 4059; (g) Wang, Z.-K.; Wu, Y.-J.; Yao, Q.-J.; Shi, B-F. *Angew. Chem. Int. Ed.* **2023**, *62*, e202304706; (h) Singh, P.; Babu, S. A.; Aggarwal, Y.; Patel, P. *Asian J. Org. Chem.* **2021**, *10*, 180; (i) Landge, V. G.; Midya, S. P.; Rana, J.; Shinde, D. R.; Balaraman, E. *Org. Lett.* **2016**, *18*, 5252; (j) Li, Q.; Zhang, S.-Y.; He, G.; Nack, W. A.; Chen, G. *Adv. Synth. Catal.* **2014**, *356*, 1544; (k) Pearson,

R.; Zhang, S.; He, G.; Edwards, N.; Chen, G. *Beilstein J. Org. Chem.* **2013**, *9*, 891; (l) Liu, P.; Han, J.; Chen, C. P.; Shi, D. Q.; Zhao, Y. S. *RSC Adv.* **2015**, *5*, 28430; (m) Martínez, Á. M.; Rodríguez, N.; Gómez-Arrayás, R.; Carretero, J. C. *Chem. Eur. J.* **2017**, *23*, 11669.

15. For selected papers on bidentate directing group-aided C-H functionalization of amino acid derivatives, see: (a) Tran, L. D.; Daugulis, O. *Angew. Chem. Int. Ed.* **2012**, *51*, 5188; (b) He, G.; Chen, G. *Angew. Chem. Int. Ed.* **2011**, *50*, 5192; (c) Xu, J.-W.; Zhang, Z.-Z.; Rao, W.-H.; Shi, B.-F. *J. Am. Chem. Soc.* **2016**, *138*, 10750; (d) Tomar, R.; Suwasia, S.; Choudhury, A. R.; Venkataramani, S.; Babu, S. A. *Chem. Commun.* **2022**, *58*, 12967; (e) Feng, R.; Wang, B.; Liu, Y.; Liu, Z.; Zhang, Y. *Eur. J. Org. Chem.* **2015**, 142; (f) Banga, S.; Kaur, R.; Babu, S. A. *Eur. J. Org. Chem.* **2021**, 3641; (g) Kaur, R.; Banga, S.; Babu, S. A. *Org. Biomol. Chem.* **2022**, *20*, 4391; (h) Kaplaneris, N.; Puet, A.; Kallert, F.; Pöhlmann, J.; Ackermann, L. *Angew. Chem. Int. Ed.* **2023**, *62*, e202216661; (i) Deb, A.; Singh, S.; Seth, K.; Pimparkar, S.; Bhaskararao, B.; Guin, S.; Sunoj, R. B.; Maiti, D. *ACS Catal.* **2017**, *7*, 8171; (j) Bisht, N.; Babu, S. A.; Tomar, R. *Asian J. Org. Chem.* **2022**, *11*, e202200589. (k) Tomar, R.; Bhattacharya, D.; Babu, S. A. *Tetrahedron* **2019**, *75*, 2447; (l) Affron, D. P.; Davis, O. A.; Bull, J. A. *Org. Lett.* **2014**, *16*, 4956.

16. For papers dealing with ortho (or) γ-C(sp^2)-H functionalization of phenylglycine type α-amino acid motifs, see: (a) Narang, U.; Singh, P.; Babu, S. A. *Eur. J. Org. Chem.* **2023**, *26*, e202300463; (b) Zeng, W.; Nukeyeva, M.; Wang, Q.; Jiang, C. *Org. Biomol. Chem.* **2018**, *16*, 598; (c) Tomar, R.; Kumar, A.; Dalal, A.; Bhattacharya, D.; Singh, P.; Babu, S. A. *Asian J. Org. Chem.* **2022**, *11*, e202200311; (d) Zhang, L.-S.; Chan, G.; Wang, X.; Guo, Q.-Y.; Zang, X.-S.; Pan, F.; Chen, K.; Shi, Z.-J. *Angew. Chem. Int. Ed.* **2014**, *53*, 3899.

17. For selected papers dealing with ortho δ-C(sp^2)−H functionalization of phenylalanine or tyrosine type α-amino acid motifs, see: (a) Wang, X.; Niu, S.; Xu, L.; Zhang, C.; Meng, L.; Zhang, X.; Ma, D. *Org. Lett.* **2017**, *19*, 246; (b) Singh, P.; Babu, S. A. *Eur. J. Org. Chem.* **2023**, e202300440; (c) Zeng, Y.; Song, W. *Org. Lett.* **2019**, *21*, 3257; (d) García-Rubia, A.; Laga, E.; Cativiela, C.; Urriolabeitia, E. P.; Gomez-Arrayás, R.; Carretero, J. C. *J. Org. Chem.* **2015**, *80*, 3321; (e) Andrade-Sampedro, P.; Matxain, J. M.; Correa, A. *Chem. Eur. J.* **2021**, *27*, 5782; (f) Zhang, S.-Y.; He, G.; Nack, W. A.; Zhao, Y.; Li, Q.; Chen, G. *J. Am. Chem. Soc.* **2013**, *135*, 2124; (g) Zhang, S.-Y.; He, G.; Zhao, Y.; Wright, K.; Nack; W. A.; Chen, G. *J. Am. Chem. Soc.* **2012**,

134, 7313; (h) Zhang, L.; Wang, C.; Han, J.; Huang, Z.-B.; Zhao, Y. *J. Org. Chem.* **2016**, *81*, 5256; (i) Zhao, F.; Jia, X.; Zhao, J.; Fei, C.; Liu, L.; Liu, G.; Wang, D.; Chen, F. *RSC Adv.* **2017**, *7*, 25031; (j) Nadres, T.; Daugulis, O. *J. Am. Chem. Soc.* **2012**, *134*, 7.

18. For paper dealing with ortho (or) γ-C(sp^2)−H functionalization of phenylglycine type α-amino acid motifs assembled *via* Ugi reaction, see: Martínez-Flores, S.; Mujica-Martinez, C. A.; Polindara-García, L. A. *Eur. J. Org. Chem.* **2022**, e202101517; (b) For a paper dealing with γ-C(sp^3)−H functionalization of glycine type motifs assembled *via* Ugi reaction, see: de León, D. A.-P.; Sánchez-Chávez, A. C.; Polindara-García, L. A. *J. Org. Chem.* **2019**, *84*, 12809.

19. (a) Ugi, I.; Werner, B.; Dömling, A. *Molecules* **2003**, *8*, 53; (b) Ugi, I.; Heck, S. *Comb. Chem. High Throughput Screen.* **2001**, *4*, 1.

20. For papers dealing with examples of C(sp^2)-H functionalization of pyrene motifs, see: (a) Odani, R.; Hirano, K.; Satoh, T.; Miura, M. *J. Org. Chem.* **2013**, *78*, 11045; (b) Dalal, A.; Babu, S. A. *Synthesis* **2021**, *53*, 3307; (c) Just-Baringo, X.; Shin, Y.; Panigrahi, A.; Zarattini, M.; Nagyte, V.; Zhao, L.; Kostarelos, K.; Casiraghi, C.; Larrosa, I. *Chem. Sci.* **2020**, *11*, 2472; (d) Rej, S.; Chatani, N. *ACS Catal.* **2018**, *8*, 6699; (e) Roy, S.; Pradhan, S.; Punniyamurthy, T. *Chem. Commun.* **2018**, *54*, 3899; (f) Iwasaki, M.; Kaneshika, W.; Tauchiya, Y.; Nakajima, K.; Nishihara, Y. *J. Org. Chem.* **2014**, *79*, 11330; (g) Ying, J.; Fu, L.-Y.; Zhong, G.; Wu, X.-F. *Org. Lett.* **2019**, *21*, 5694; (h) Gao, Y.; Zhang, M.; Wang, C.; Yang, Z.; Huang, X.; Feng, R.; Qi, C. *Chem. Commun.* **2020**, *56*, 14231; (i) Asako, S.; Ilies, L.; Nakamura, E. *J. Am. Chem. Soc.* **2013**, *135*, 17755; (j) Luo, A.; Zhang, M.; Fu, Z.; Lan, J.; Wu, D.; You, J. *Beilstein J. Org. Chem.* **2020**, *16*, 530.

21. For papers dealing with examples of C(sp^2)-H functionalization of pyrene motifs, see: (a) Sire, C.; Cattey, H.; Tsivery, A.; Hierso, J.-C.; Roger, J. *Adv. Synth. Catal.* **2022**, *364*, 440; (b) He, Y.-Q.; Zhong, Y.-W. *Chem. Commun.* **2015**, *51*, 3411; (c) Niu, Y.; Qi, Z.; Lou, Q.; Bai, P.; Yang, S. *Chem. Commun.* **2020**, *56*, 14721; (d) Coventry, D. N.; Batsanov, A. S.; Goeta, A. E.; Howard, J. A. K.; Marder, T. B.; Perutz, R. N. *Chem. Commun.* **2005**, 2172. For a recent review dealing with C-H functionalization of pyrenes, see: (e) Babu, S. A.; Dalal, A.; Bodak, S. *Chemistry* **2023**, *5*, 2713.

22. (a) Song, J.; Chen, W.; Zhao, Y.; Li, C.; Liang, G.; Huang, L. *RSC Adv.* **2016**, *6*, 54984; (b) Rajkumar, V.; Naveen.; Babu, S. A. *ChemistrySelect* **2016**, *1*, 1207; (c) Singh, P.; Dalal, A.; Babu, S. A. *Asian J. Org. Chem.* **2019**, *8*, 877; (d) Pasunooti, K.

K.; Banerjee, B.; Yap, T.; Jiang, Y.; Liu, C.-F. *Org. Lett*. **2015**, *17*, 6094; (e) Donovan, D. H. O'.; Fusco, C. D.; Spring, D. R. *Tetrahedron Lett*. **2016**, *57*, 2962.

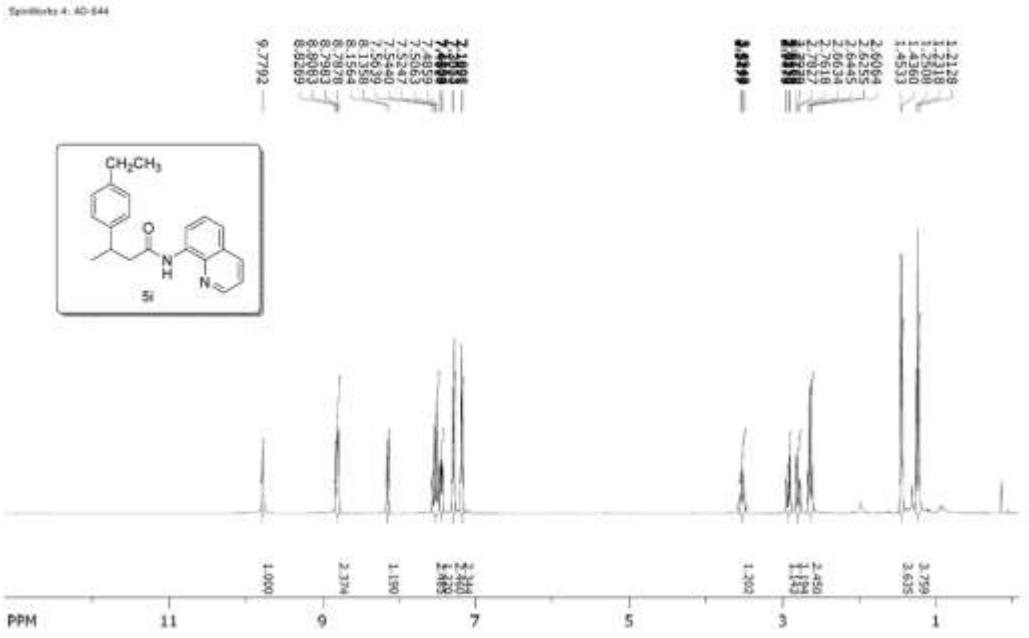
22. UV-Vis absorption (λ_{max} (nm)) value for compounds, **4a:** 347, **4b:** 347, **4c:** 347, **4d:** 347, **6a:** 351, **6b:** 350, **6c:** 351, **6d:** 350, **6e:** 351, **6f:** 351, **6g:** 351, **6h:** 351, **6i:** 350, **6j:** 350, **6k:** 351, **6l:** 351, **6m:** 351, **6n:** 351, **6o:** 351, **6p:** 351, **6q:** 353, **6r:** 351, **6s:** 351, **6t:** 350, **6u:** 351, **6v:** 351, **6w:** 351, **6x:** 351, **6y:** 350, **6z:** 351, **6za:** 351, **6zb:** 351, **6zc:** 350, **6zd:** 349, **6ze:** 351, **6zf:** 349, **7a:** 353, **7b:** 350, **7c:** 349, **7d:** 353, **7e:** 350, **7f:** 352, **7g:** 349, **7h:** 349, **8a:** 350, **8b:** 350, **8c:** 350, **8d:** 350, **8e:** 350, **8f:** 350, **8f-(D):** 350, **8g:** 350, **8h:** 350, **6zg:** 350, **6zh:** 350, **6zi:** 350, **6zj:** 350, **6zk:** 350, **6zl:** 350 (nm).

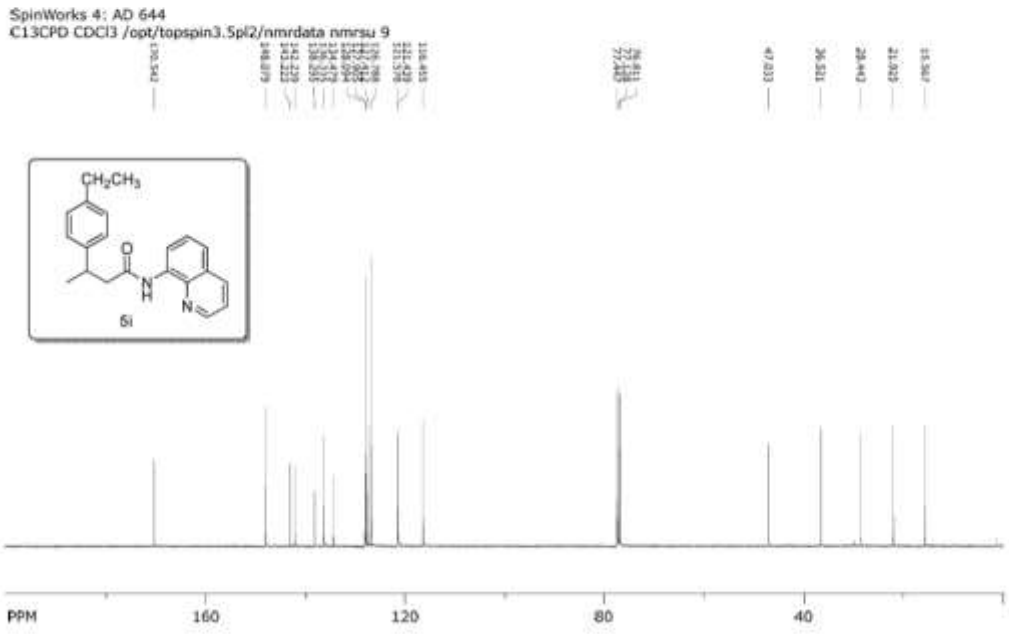
23. Li, P.-F.; Chen, C.-F. *J. Org. Chem*. **2012**, *77*, 9250. (b) Bair, K. W.; Andrews, C. W.; Tuttle, R. L.; Knick, V. C.; Cory, M.; McKee, D. D. *J. Med. Chem.* **1991**, *34*, 1983.

24. While a single signal is expected, there seems to be the existence of rotamers; thus, more than one signal is observed. For a related paper dealing with rotamers with aryl compounds containing F, see: Sun, M.; Chen, W.; Zhang, T.; Liu, Z.; Wei, J.; Xi, N. *Tetrahedron* **2020**, *76*, 131679.

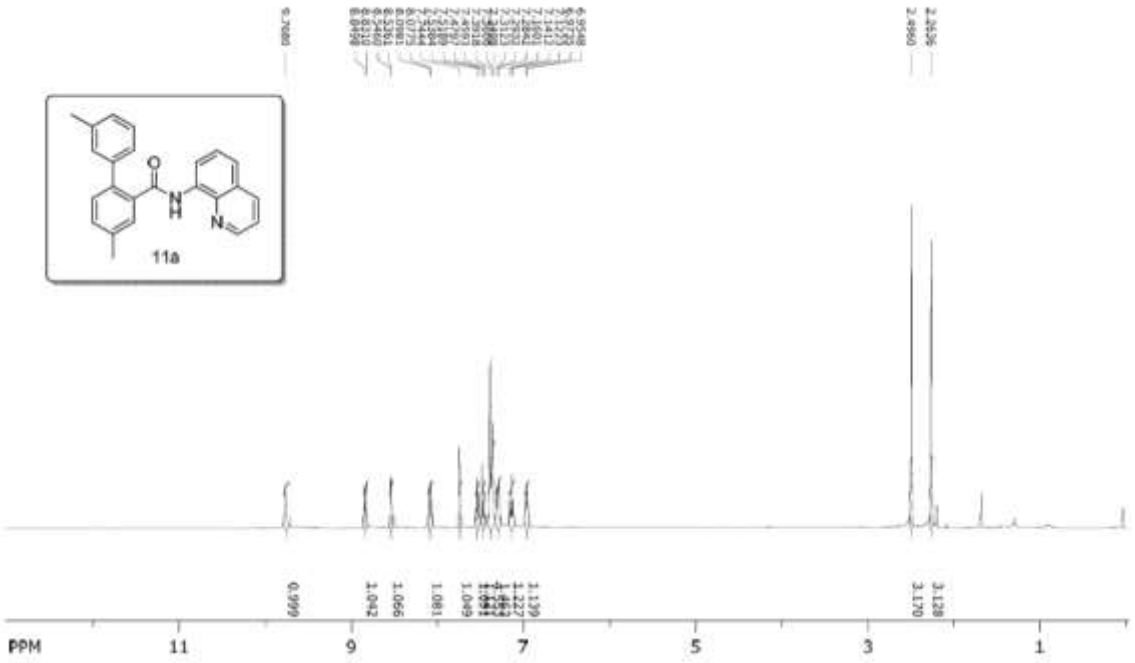
Appendix Section. Representative NMR-Spectra

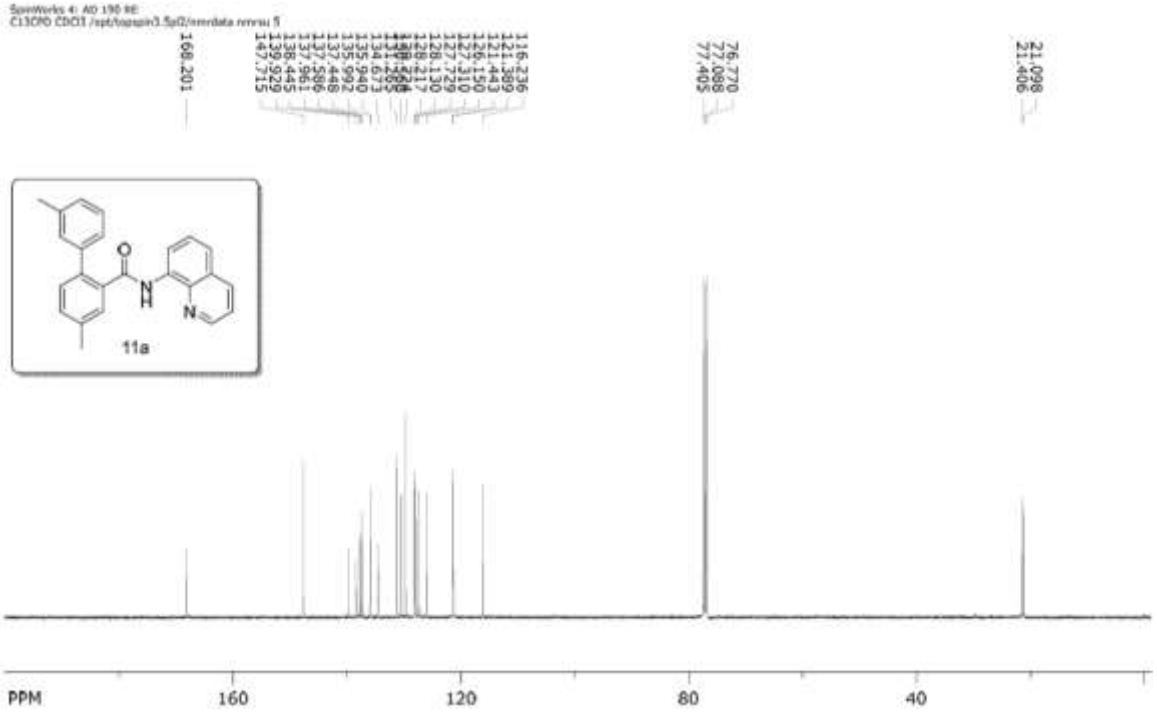
Chapter 2:

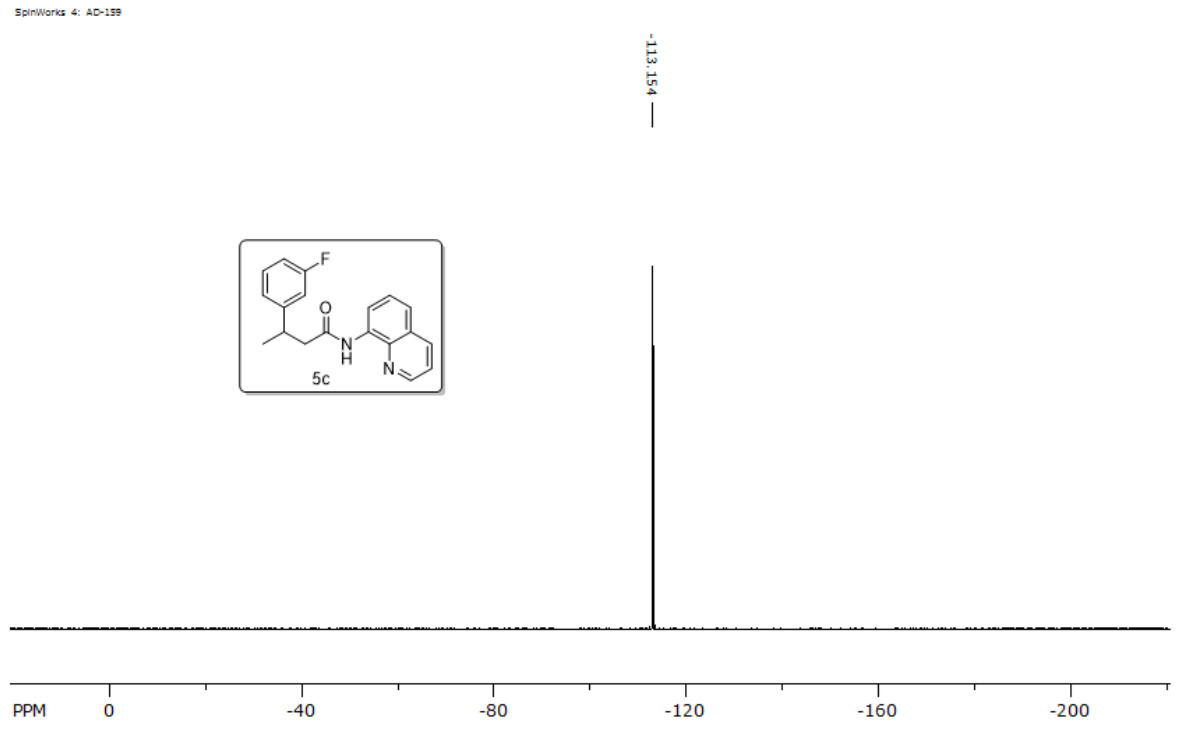




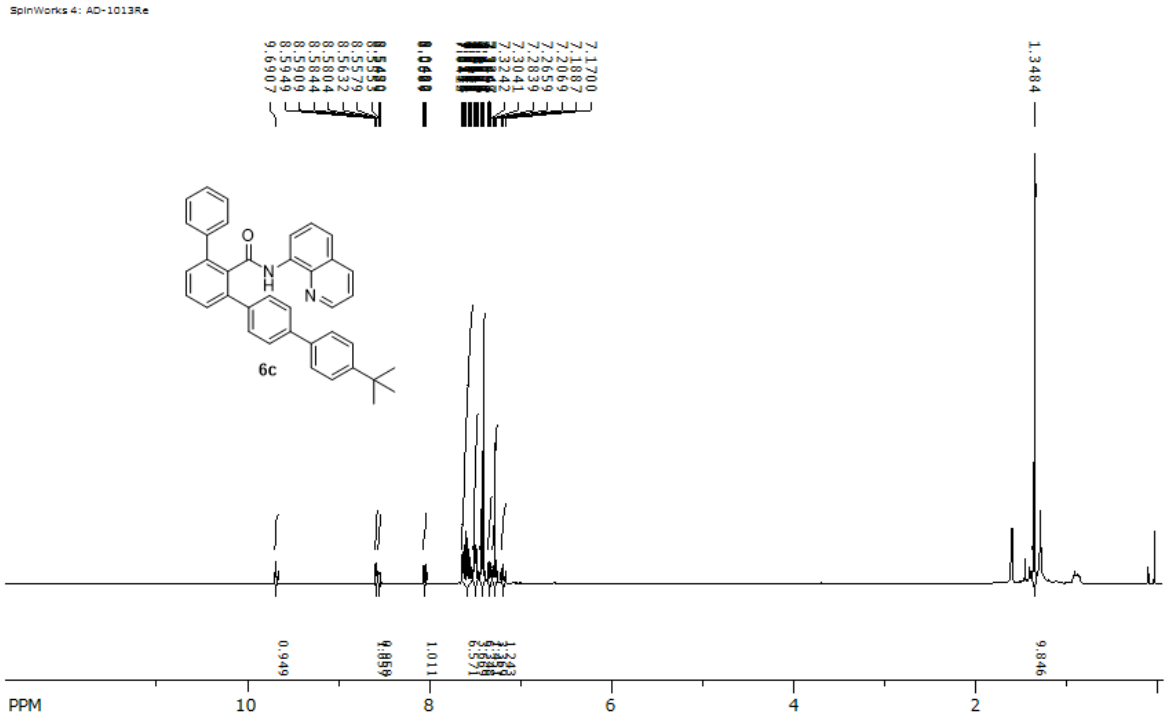
SpinWorks 4: ad 190

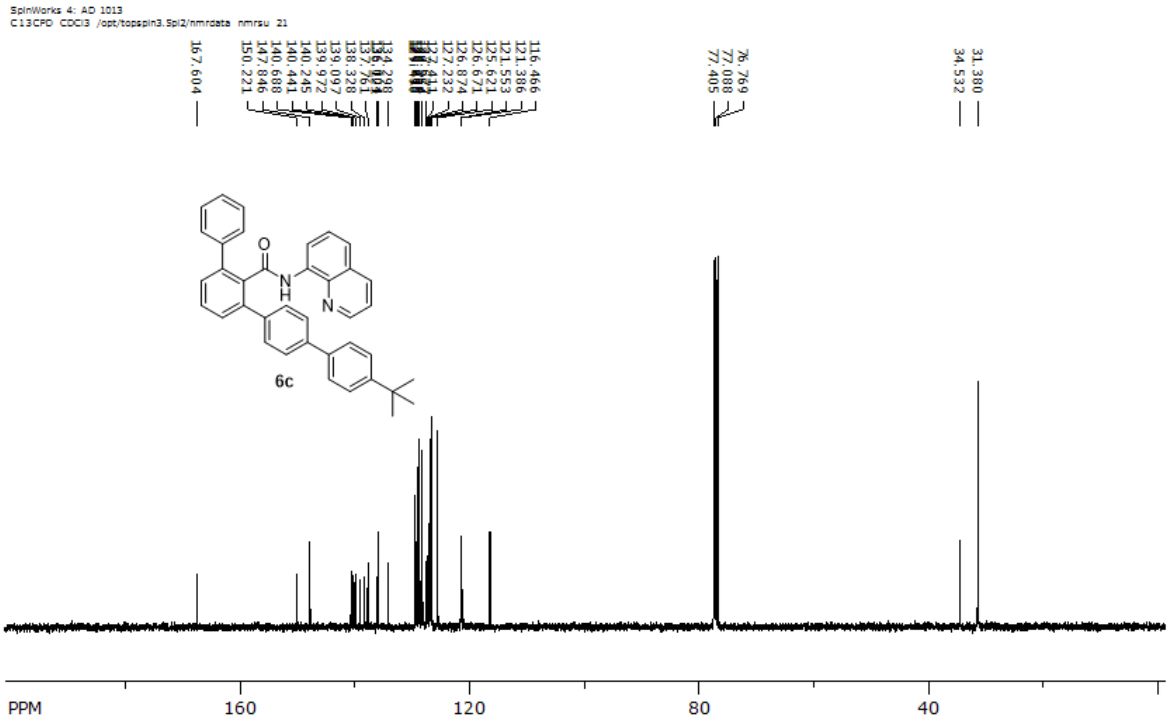


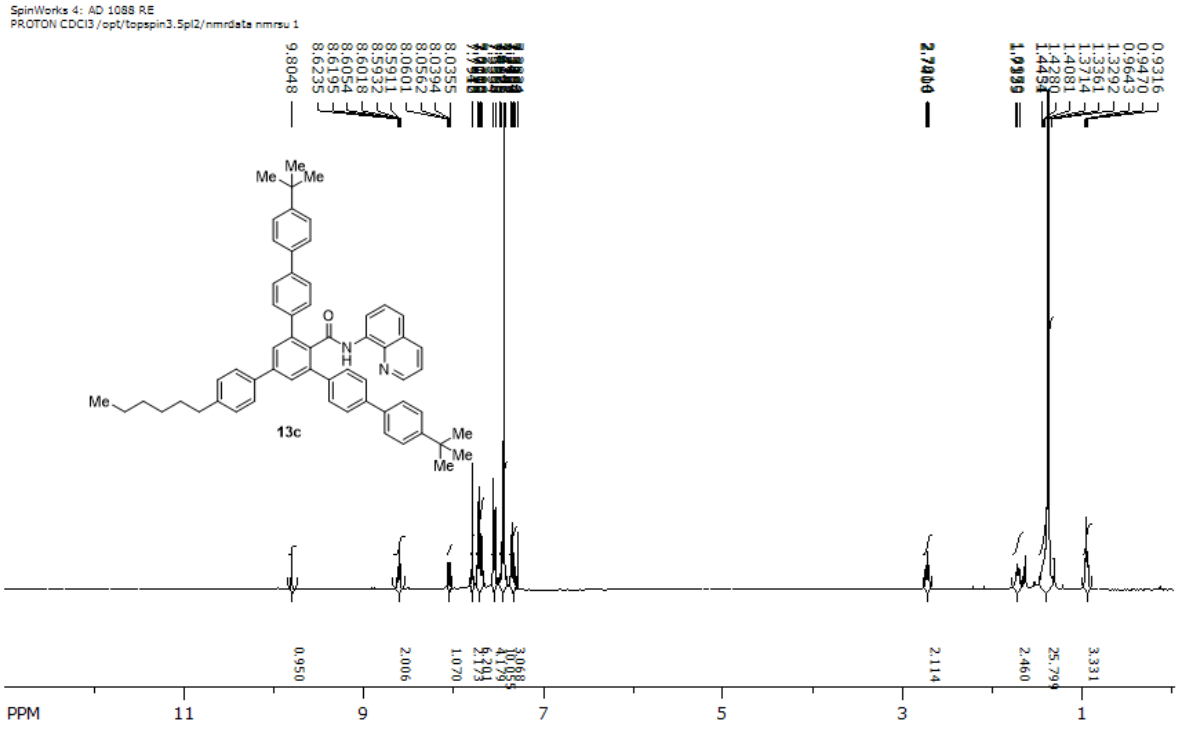


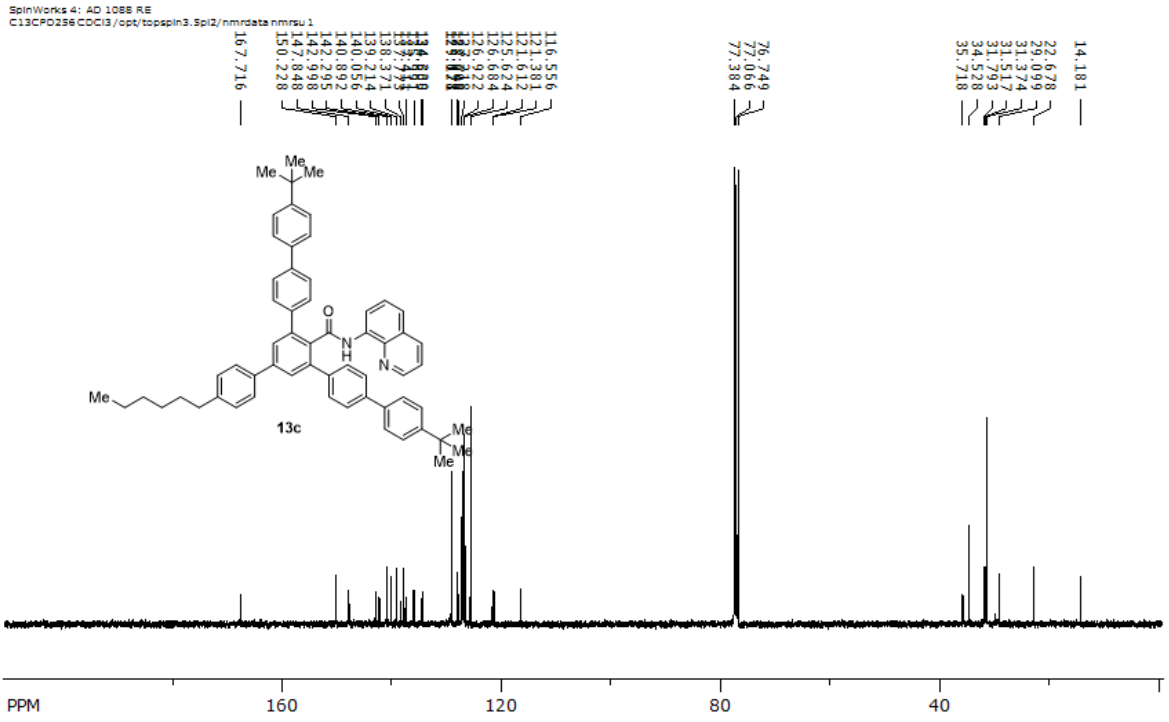

SpinWorks 4: AD-159
-113.154
F
O
N
H
N
5c
PPM
0
-40
-80
-120
-160
-200

Chapter 3:

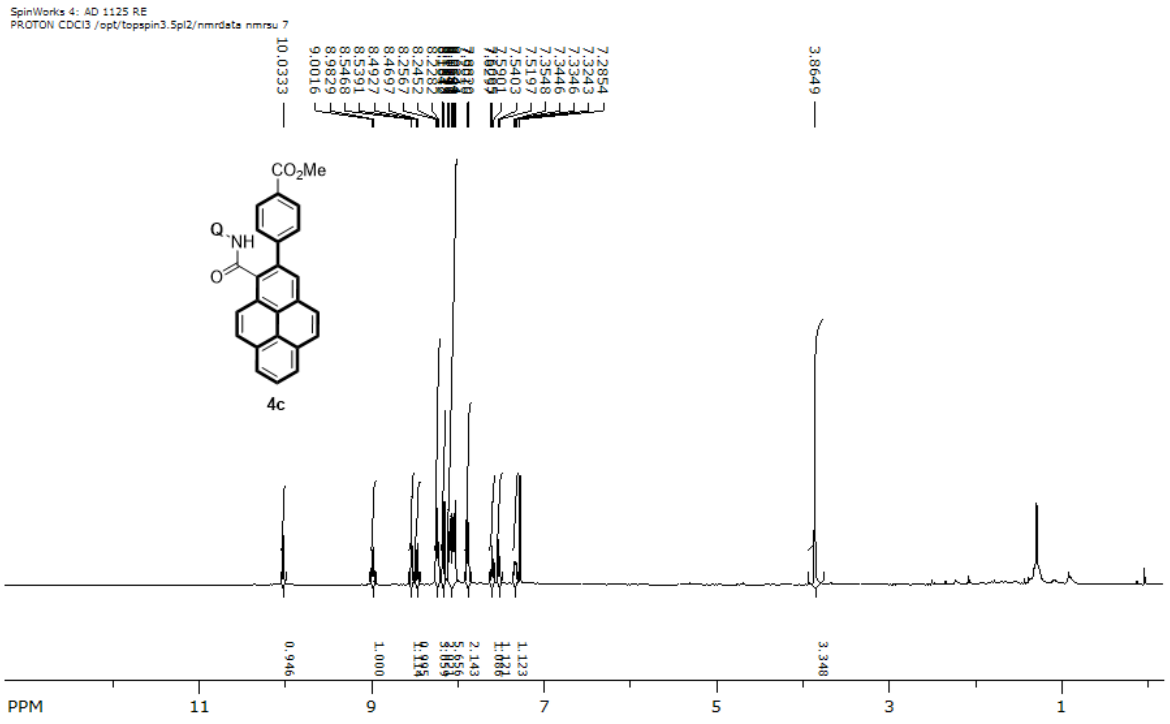

SpinWorks 4: AD-1013Re
9.6907
8.5949
8.5809
8.5804
8.5644
8.5632
8.5579
7.3242
7.3041
7.2839
7.2069
7.1887
7.1700
1.3484
6c
0.949
1.011
9.846
PPM
10
8
6
4
2

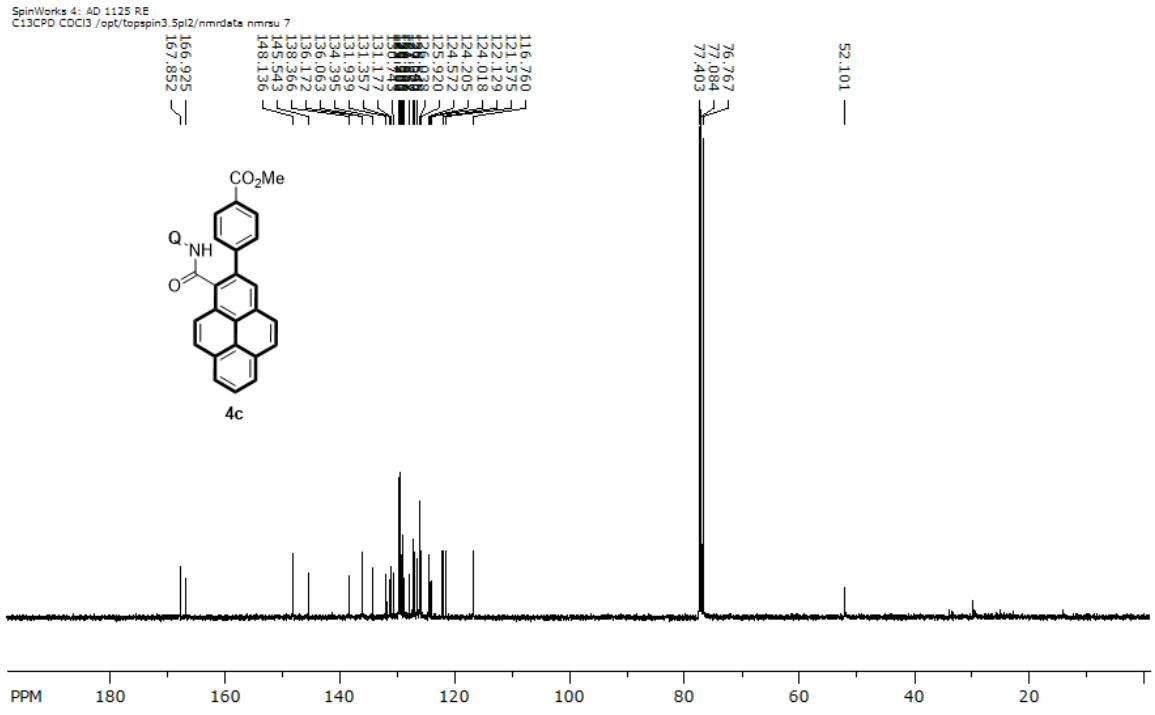

SpinWorks 4: AD 1013
C13CPD CDCl3 /opt/topspin3.5pl2/nmrdata nmrsu 21
167.604
150.221
147.846
140.688
140.441
140.245
139.972
139.097
138.328
116.466
121.386
121.553
125.621
126.671
126.874
127.232
77.405
77.088
76.769
34.532
31.380
6c
PPM
160
120
80
40

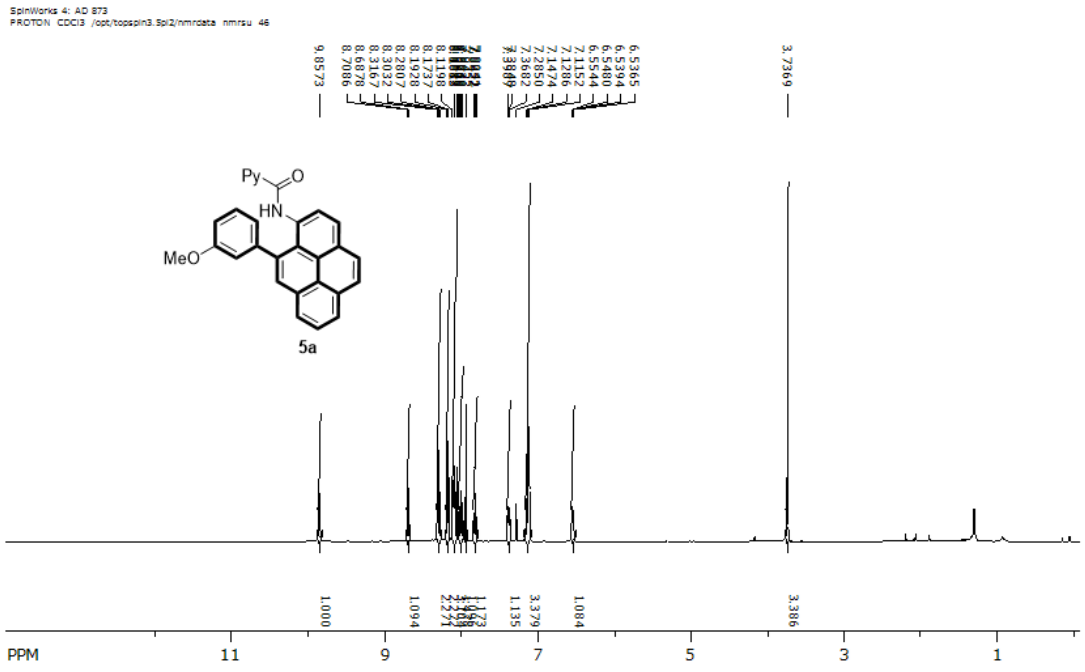

SpinWorks 4: AD 1088 RE
PROTON CDCl3 /opt/topspin3.5pl2/nmrdata nmrsu 1
13c
PPM

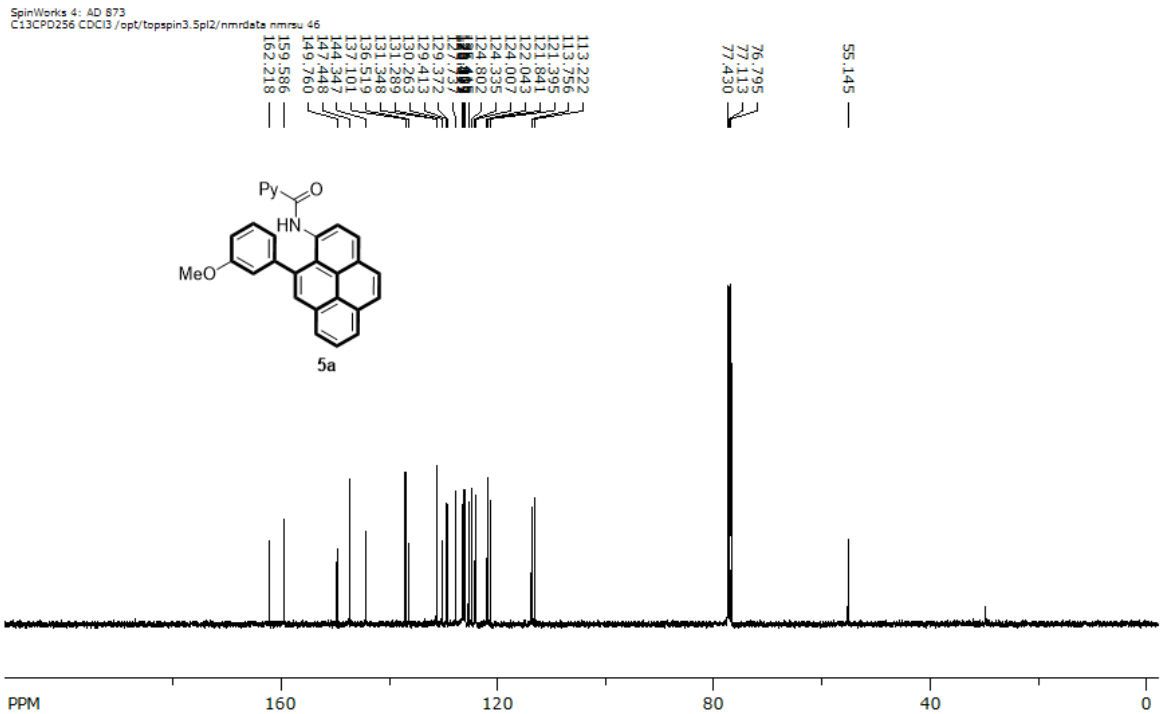

SpinWorks 4: AD 1088 RE
C13CPD256 CDCl3 /opt/topspin3.5pl2/nmrdata nmrsu 1
13c
PPM

Chapter 4:

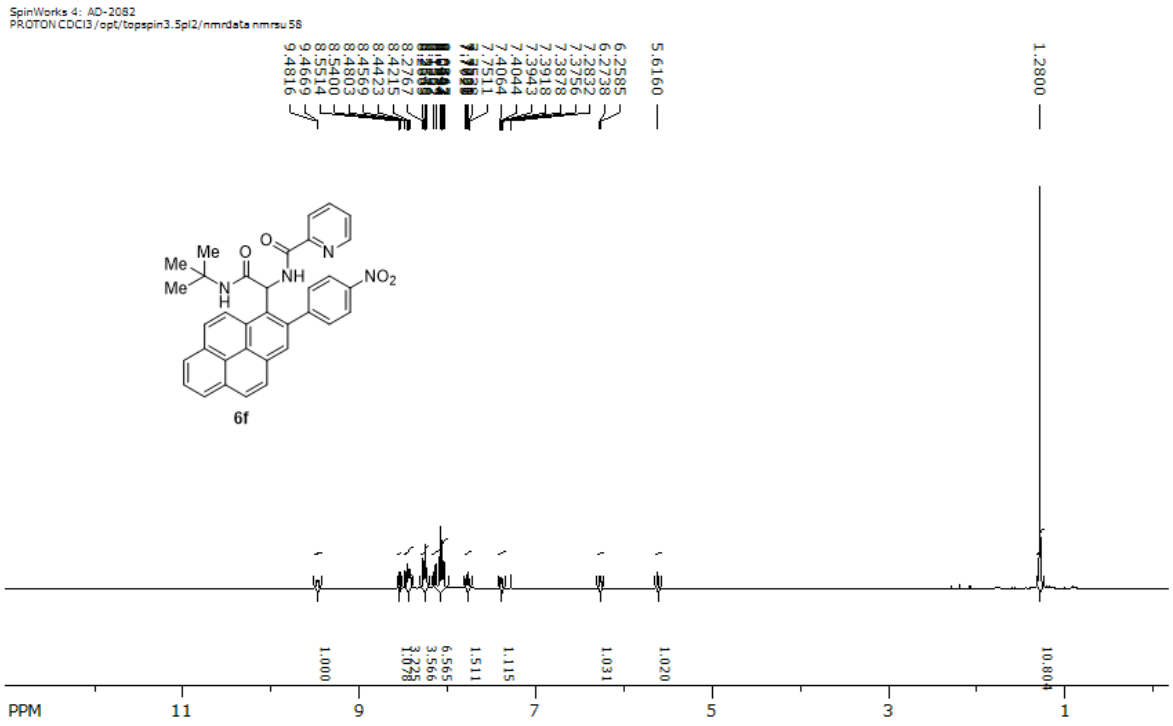

SpinWorks 4: AD 1125 RE
PROTON CDCl3 /opt/topspin3.5pl2/nmrdata nmrsu 7
10.0333
9.0016
8.9829
8.5468
8.5391
8.4927
8.4697
8.2567
8.2452
7.2854
7.5403
7.5197
7.3548
7.3446
7.3346
7.3243
3.8649
CO2Me
NH
O
4c
0.946
1.000
2.143
1.123
3.348
PPM
11
9
7
5
3
1

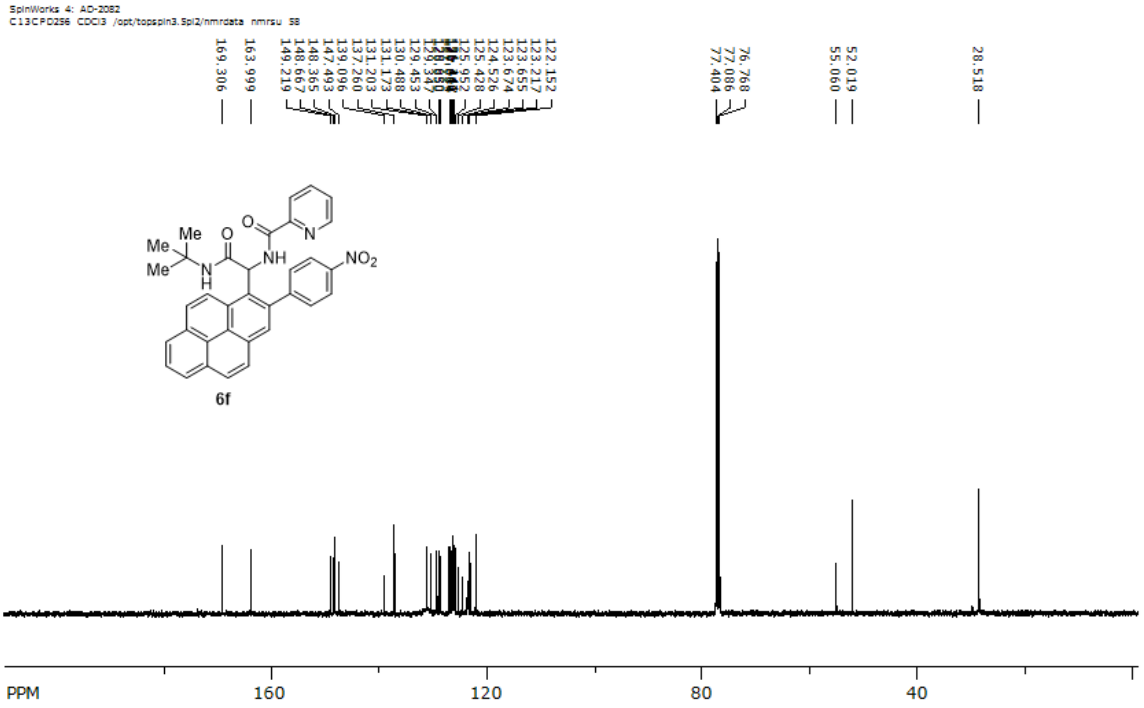

SpinWorks 4: AD 1125 RE
C13CPD CDCl3 /opt/topspin3.5pl2/nmrdata nmrsu 7
166.925
167.852
148.136
145.543
138.366
136.172
136.063
134.395
131.939
131.357
131.177
116.760
121.575
122.129
124.018
124.205
124.572
125.926
76.767
77.084
77.403
52.101
CO2Me
NH
O
4c
PPM
180
160
140
120
100
80
60
40
20

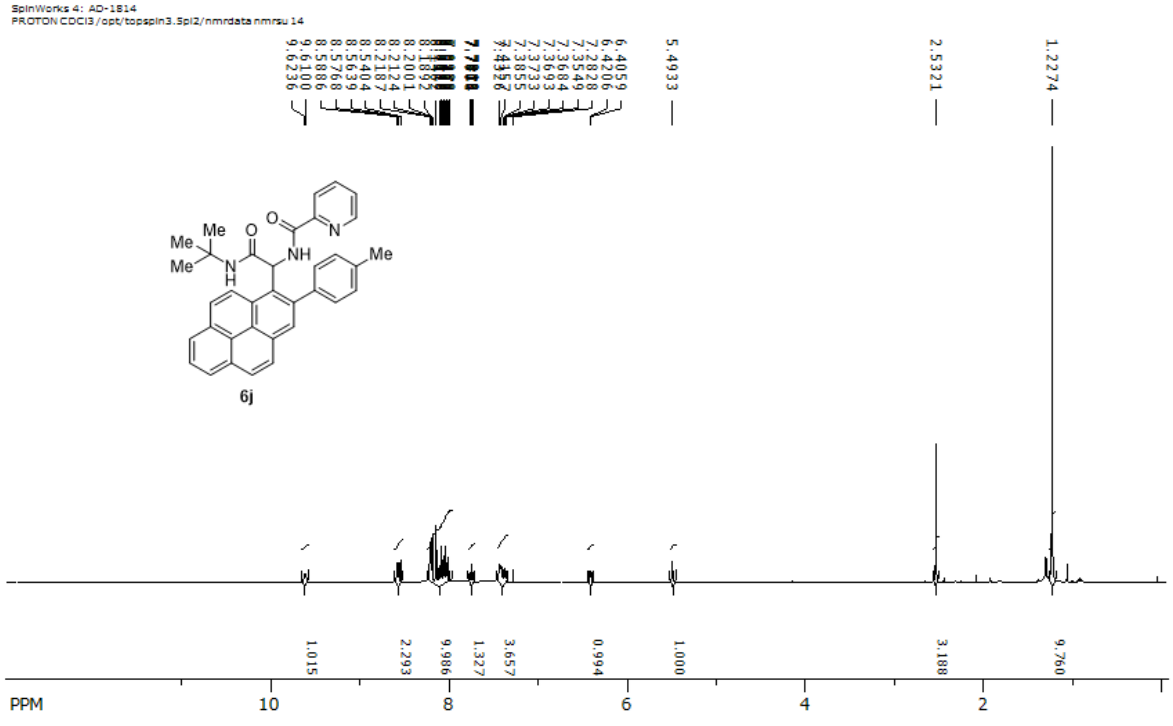

SpinWorks 4: AD 873
PROTON CDCl3 /opt/topspin3.5pl2/nmrdata nmrsu 46
9.8573
8.7066
8.6878
8.3167
8.3032
8.2807
8.1928
8.1737
8.1198
7.3682
7.2850
7.1474
7.1286
7.1152
6.5544
6.5480
6.5394
6.5365
3.7369
Py
O
HN
MeO
5a
1.000
1.094
1.135
3.379
1.084
3.386
PPM
11
9
7
5
3
1

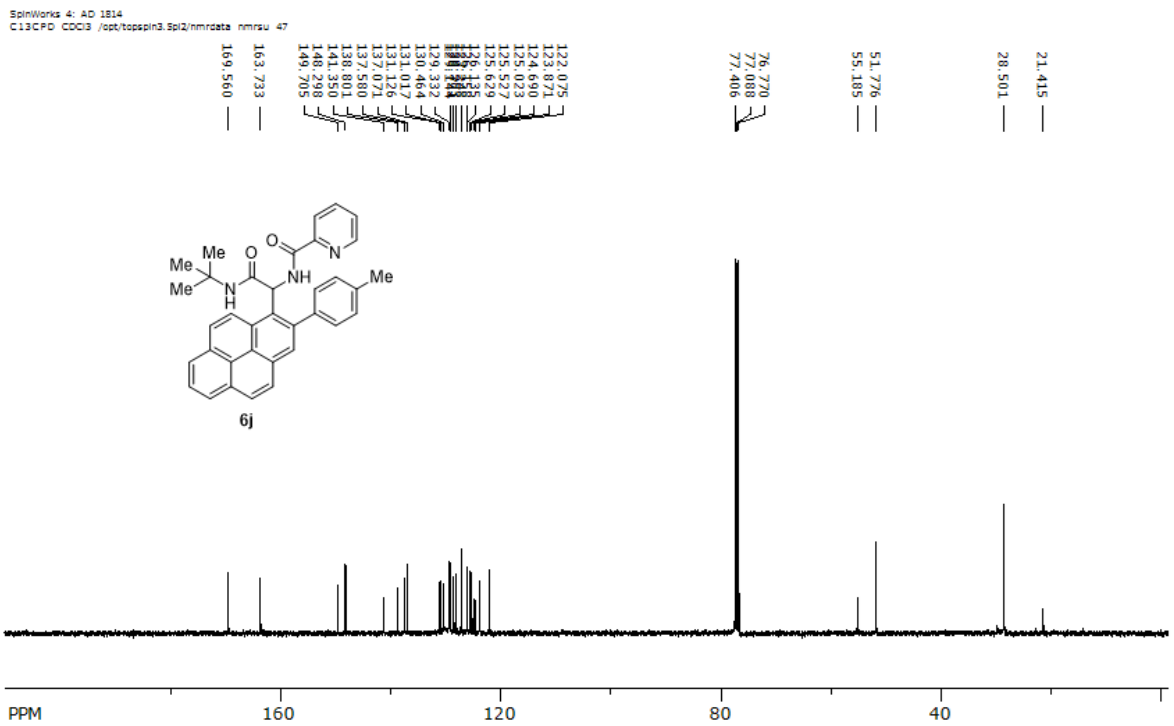

SpinWorks 4: AD 873
C13CPD256 CDCl3 /opt/topspin3.5pl2/nmrdata nmrsu 46
162.218
159.586
149.760
147.448
144.347
137.101
136.519
131.348
131.289
130.263
129.413
129.372
124.335
124.007
122.043
121.841
121.395
113.766
113.222
77.430
77.113
76.795
55.145
Py
O
HN
MeO
5a
PPM
160
120
80
40
0

Chapter 5:


SpinWorks 4: AD-2082
PROTON CDCl3 /opt/topspin3.5pl2/nmrdata nmrsu 58
9.4816
9.4669
8.5514
8.5400
8.4803
8.4569
8.4423
8.4215
8.2767
7.9964
7.4044
7.3943
7.3918
7.3878
7.3756
7.2832
6.2585
6.2738
5.6160
1.2800
Me
Me
N
H
O
NH
N
NO2
6f
1.000
3.078
3.566
6.565
1.511
1.115
1.031
1.020
10.804
PPM
11
9
7
5
3
1


SpinWorks 4: AD-2082
C13CPD256 CDCl3 /opt/topspin3.5pl2/nmrdata nmrsu 58
169.306
163.999
149.219
148.667
148.365
147.493
139.096
137.280
131.203
131.173
130.488
129.453
125.952
125.428
124.526
123.655
123.674
123.217
122.152
77.404
77.086
76.768
55.060
52.019
28.518
Me
Me
N
H
O
NH
N
NO2
6f
PPM
160
120
80
40


SpinWorks 4: AD-1814
PROTON CDCl3 /opt/topspin3.5pl2/nmrdata nmrsu 14
9.6236
9.6100
8.5986
8.5768
8.5539
8.5404
8.2187
8.2124
8.2001
7.4426
7.3855
7.3733
7.3693
7.3664
7.3549
7.2828
6.4206
6.4059
5.4933
2.5321
1.2274
Me
Me
O
N
NH
Me
6j
1.015
2.293
9.986
1.327
3.657
0.994
1.000
3.188
9.760
PPM
10
8
6
4
2


SpinWorks 4: AD 1814
C13CPD CDCl3 /opt/topspin3.5pl2/nmrdata nmrsu 47
169.560
163.733
149.705
148.298
141.350
138.801
137.580
137.071
131.126
131.017
130.464
129.332
125.629
125.527
125.023
124.693
123.871
122.075
77.406
77.088
76.770
55.185
51.776
28.501
21.415
Me
Me
O
N
NH
Me
6j
PPM
160
120
80
40