Studies on Pd(II)-Catalyzed C-H Functionalization of Benzyl Amine, Phenylglycinol, Phenylalaninol, Tyrosine, and ortho-Toluidine Compounds

A thesis submitted for the partial fulfilment
of the degree of Doctor of Philosophy

By

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Dedicated to

Beloved Parents,

Family and Friends

Declaration

I hereby declare that matter embodied in this thesis entitled **''Studies on Pd(II)-Catalyzed C-H Functionalization of Benzyl Amine, Phenylglycinol, Phenylalaninol, Tyrosine, and *ortho*-Toluidine Compounds''** 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.

Prabhakar Singh

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

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Place:

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List of the publications from this thesis work:

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

Title: Pd(II)-catalyzed sp^3/sp^2 γ- and δ-C-H functionalization of aryl amines using 5-methylisoxazole-3-carboxamide as directing group.

2. **Singh, P**.; Babu, S. A.*; Aggarwal, Y.; Patel, P. *Asian J. Org. Chem*. **2021**, *10*, 180.

Title: Pd(II)-catalyzed picolinamide-aided sp^2 γ- C-H functionalization of phenylglycinol: access to γ- C-H arylated, alkylated and halogenated phenylglycinol scaffolds.

3. Bisht, N.#; **Singh, P**.#; Babu, S. A.* *Synthesis* **2022**, *54*, 4059. (# = authors contributed equally)

Title: Pd(II)-catalyzed picolinamide-aided γ-C(sp^2)-H functionalization of racemic and enantiopure α-methylbenzylamine and phenylglycinol scaffolds.

4. Narang, U #.; **Singh, P** #., Babu, S. A.* *Eur. J. Org. Chem*. **2023**, e202300463. (# = authors contributed equally)

Title: Construction of β-phenylalanine derivatives *via* Pd-catalyzed C(sp^2)-H (*ortho*) functionalization.

5. **Singh, P**.; Babu, S. A.* *Eur. J. Org. Chem*. **2023**, e202300440.

Title: Pd-catalyzed arylation and benzylation of tyrosine at the δ-C(sp^2)-H and C(2) positions: expanding the library of unnatural tyrosines.

6. **Singh, P**.; Babu, S. A.* *Synthesis* **2023**, *55*, A-AF.

Title: Pd(II)-catalyzed remote δ-C(sp^2)-H functionalization in phenylalaninols: expanding the library of phenylalaninols.

List of publications as co-author:

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.

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. 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.

4. Aggarwal, Y. [#]; Padmavathi, R. [#]; **Singh, P**.; Babu, S. A.[*] *Asian J. Org. Chem*. **2022**, *11*, e202200327. (# = authors contributed equally)

Title: Pd(II)-catalyzed, γ-C(sp^2)-H alkoxylation in α-methylbenzylamine, phenylglycinol, 3-amino-3-phenylpropanol toward enantiopure aryl alkyl ethers.

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. Poster Presentation entitled ‘‘Pd(II)-catalyzed sp^3/sp^2 γ- and δ-C-H functionalization of aryl amines using 5-methylisoxazole-3-carboxamide as directing group’’ at the *XV Junior National Organic Symposium Trust (J-NOST)* held at Department of Chemistry, University of Delhi, Delhi-110007, India (18-21 October, 2019).
3. Poster Presentation entitled ‘‘Pd (II)-catalyzed sp^3/sp^2 γ- and δ-C-H functionalization of aryl amines using 5-methylisoxazole-3-carboxamide as directing group’’ at the 1st *CRIKC Chemistry Symposium (CCS 2019)* held at IISER Mohali, India (2-3 November, 2019).
4. Participated in the *27th CRSI-National Symposium in Chemistry,* held at Indian Institute of Science Education and Research Kolkata, India (26-29 September, 2021).
5. Participated in the 29*th CRSI-National Symposium in Chemistry*, held at Indian Institute of Science Education and Research Mohali, India (7-9 July, 2022).
6. Participated in the *Recent Advances in Bioorganic and Medicinal Chemistry (RABMC 2022)* held at National Institute of Pharmaceutical Education and Research (NIPER) Mohali, India (19th November, 2022).

Preamble

Traditional cross-coupling was an outstanding method for the C-C and C-X bond formation reactions. In particular, Suzuki, Heck, and Negishi cross-coupling reactions have gained special attention due to their widespread applications in academia and industry. A Nobel Prize was awarded to Suzuki, Heck, and Negishi in 2010 for their contribution to the cross-coupling reactions. However, these reactions have a few obvious limitations, such as the requirement of pre-functionalized starting materials, generation of waste chemicals etc. The functionalization of organic molecule *via* the C-H activation process is an effective tool for achieving C-H functionalization as pre-functionalized starting material can be avoided. Inspired by its benefits and efficacy, this thesis intends to functionalize amino alcohol, amino acid, and aryl amines *via* palladium-catalyzed bidentate directing group-assisted C-H bond functionalization.

Chapter 1 reveals the concepts of C-H activation, its significance, associated methods, and mechanistic features. Since the majority of the thesis focuses on picolinamide directed C-H functionalization of amino alcohol and aryl amines, some literature reports on picolinamide directed C-H activation as well as some C-H functionalization reports on amino alcohols have been discussed.

Chapter 2 deals with Pd(II)-catalyzed, picolinamide directed C-H functionalization of *α*-methylbenzylamine and phenylglycinol scaffolds. We have synthesized various racemic and enantiopure C-H arylated, alkylated, halogenated, benzylated phenylgycinol and *α*-methylbenzylamine motifs. The racemic and enantiopure derivatives of phenylglycinol and *α*-methylbenzylamine serve as essential building blocks in organic synthesis and medicinal chemistry. As a result, our study contributes to expanding the library of *α*-methylbenzylamine and phenylglycinol motifs.

Chapter 3 disclosed the synthesis of unnatural tyrosine-based biaryls and diarylmethanes *via* Pd(II)-catalyzed intermolecular C-H activation strategy. We have also synthesized some tyrosine-based peptides after removal of picolinyl moiety. Tyrosine derivatives are important molecules from medicinal chemistry point of view, so this work contributed to expanding the library of unnatural tyrosine motifs.

Chapter 4 deals with various *δ*-C(sp^2)-H arylated, alkylated, halogenated, and alkenylated phenylalaninol scaffolds *via* Pd(II)-catalyzed C-H functionalization. We have carried out our protocol in racemic and enantiopure substrates without disturbing the chirality of the

molecules. We have also shown synthetic utility by preparing some modified Matijin-Su (aurantiamide) derivatives using bis *ortho* C-H arylated phenylalaninol.

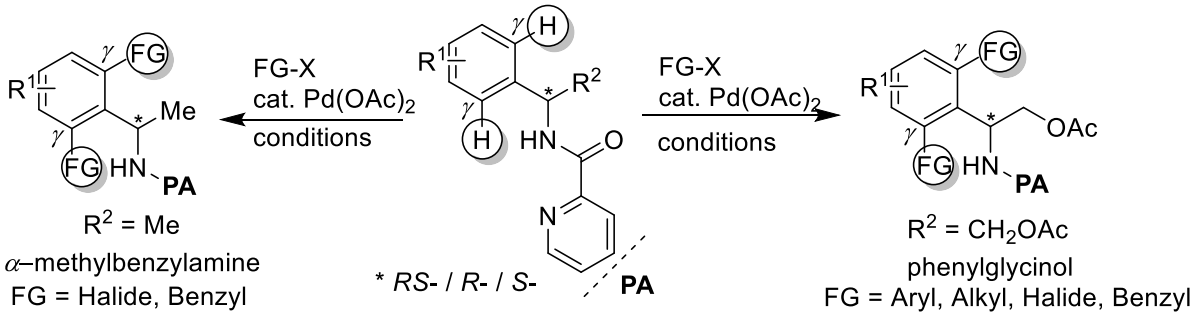
Chapter 5 focuses on the synthesis of *ortho* C-H arylated *β*-phenylalanines and 3-amino-3-phenylpropanols (1, 3-amino alcohols) through Pd(II)-catalyzed picolinamide aided C-H functionalization. Various biaryl or terphenyl type *β*-phenylalanine motifs were prepared using C-H functionalization strategy. Furthermore, after removing the picolinyl group, some synthetic modifications were carried out, such as the attachment of an amino acid moiety with *γ*-C(sp^2)-H arylated *β*-phenylalanines.

Chapter 6 describes a dual objective-based study, where 5-methylisoxazole-3-carboxamide (MICA) aided C-H functionalization in different aryl amines moieties were achieved. This process indirectly helped in assembling MICA motifs. MICA aided C-H arylation/acetoxylation of *ortho*-toluidines produced various 2-aminodiphenylmethanes and 2-aminobenzyl acetates, respectively. We have also investigated MICA aided C-H arylation/acetoxylation of benzylamines. Later, we also explored C-H amidation/alkenylation in phenylethylamine moiety.

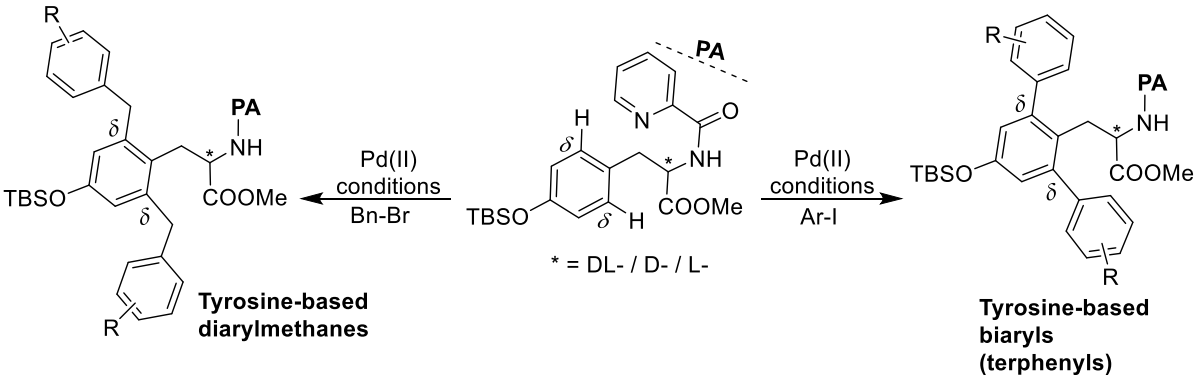
Objective

The objectives of the thesis work are listed below:

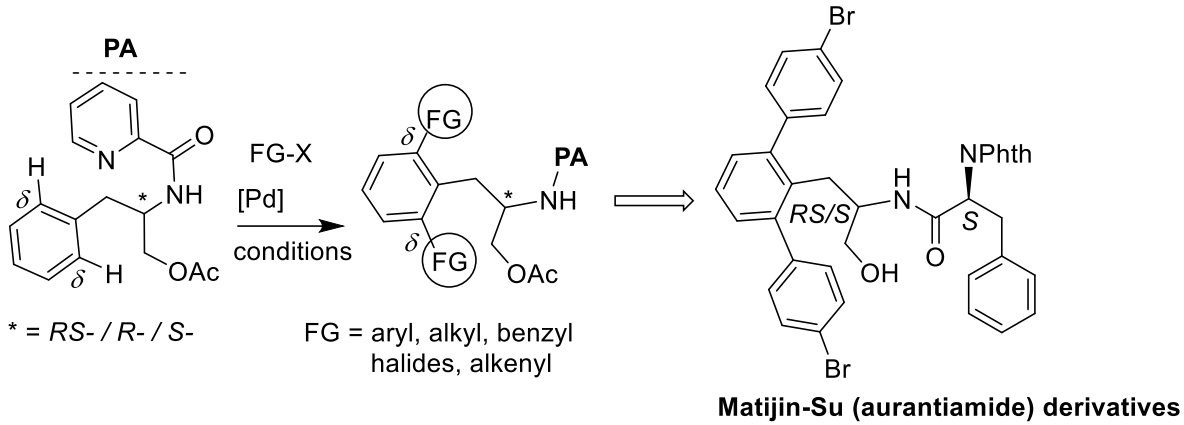
Phenylglycinol and α-methylbenzylamine scaffolds are important molecules in organic synthesis and medicinal chemistry. They are present in various drug/bio-active molecules. These molecules are used as chiral auxiliaries and building blocks in synthesizing bioactive molecules. Due to their significant properties, the C-H functionalization of the phenylglycinol and α-methylbenzylamine scaffolds is the focus of this part of the thesis.



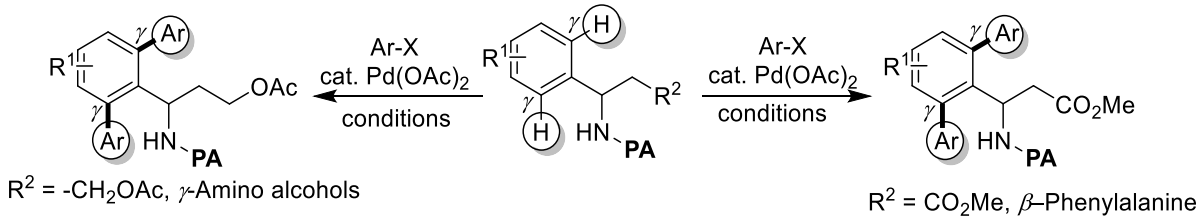
Tyrosine motifs are vital in alkaloids, peptides, and medicinal chemistry. Due to their phenolic unit, it is also used as a probing tool and as an attractive target for post-translational modifications in peptides and proteins. Encouraged by its prevalence and importance, this part of the thesis focuses on constructing unnatural biaryl and diarylmethane tyrosines.



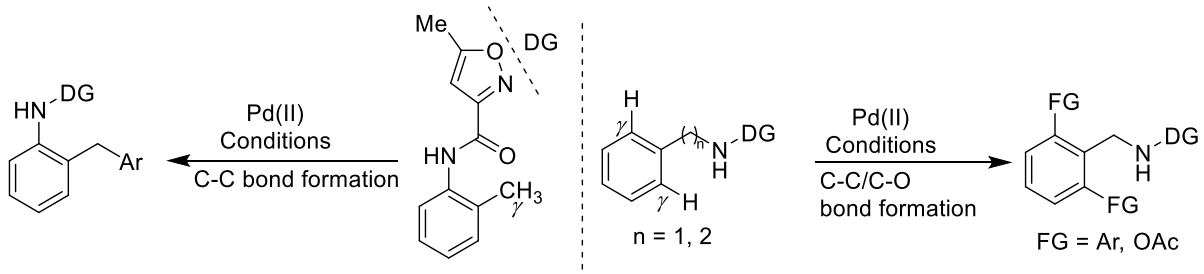
Phenylalaninol scaffolds are used as building blocks for synthesizing medicinally important compounds. Further, various phenylalaninol moieties have been used as auxiliaries and chiral ligands. Given the significance of enantiopure/racemic phenylalaninols, Pd(II)-catalyzed C-H functionalization strategy has been utilized in this chapter to modify phenylalaninols.



β-Amino acids derivatives have received particular attention in chemical and biological sciences as they are present in numerous bioactive molecules and natural products. It is an important precursor in synthesizing medicinally active molecules, including peptides. In conjunction with this, 3-amino-3-phenylpropanols, which are 1, 3-amino alcohol family members and derivatives of *β*-phenylalanines, are versatile building blocks in synthesizing medicinally active molecules. A part of this thesis focused on synthesizing some unnatural *β*-amino acid derivatives *via* Pd(II)-catalyzed C-H functionalization.



5-Methylisoxazole carboxamide (MICA) based molecules exhibit different biological activities such as irreversible human rhinovirus 3C protease inhibitors, DFG-out p38α inhibitors etc. Considering the significance of MICA motifs, this section of thesis expands the library of MICA motifs *via* C-H functionalization of *o*-toluidines, benzylamines, and phenylethylamines moiety.

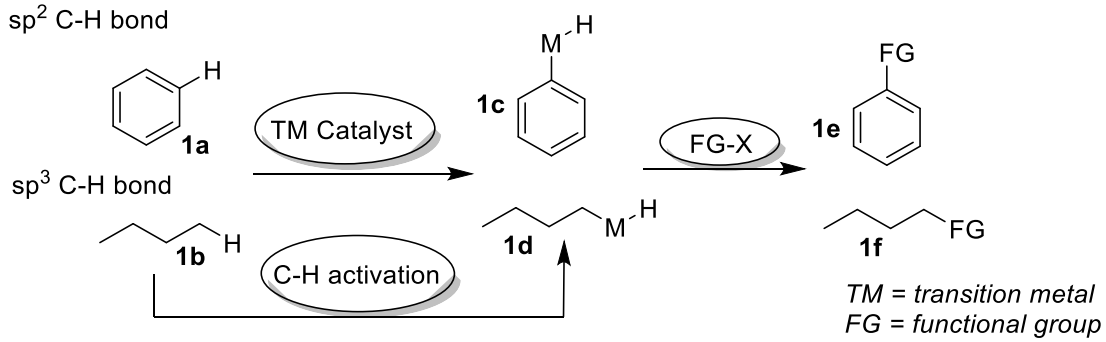


INTRODUCTION

Cross-coupling is the most beneficial and adaptable synthetic tool for organic chemists in industry and academics. Several cross-coupling methods exist[1] such as Suzuki, Heck, Negishi, Kumada, Sonogashira Stille, and Hiyama coupling. It is the coupling between a pre-functionalized precursor and aryl halides to afford the corresponding cross-coupled product. A Nobel Prize in Chemistry was awarded to R. F. Heck, E.-i. Negishi, and A. Suzuki in 2010 as a result of the success of this cross-coupling reactions. Generally, Cross-coupling reactions have been extensively used in the industry and the academic field. These methods have some limitations such as the requirement of pre-functionalized starting materials, stoichiometric waste generation, regioselectivity issues, and self-condensation products etc.

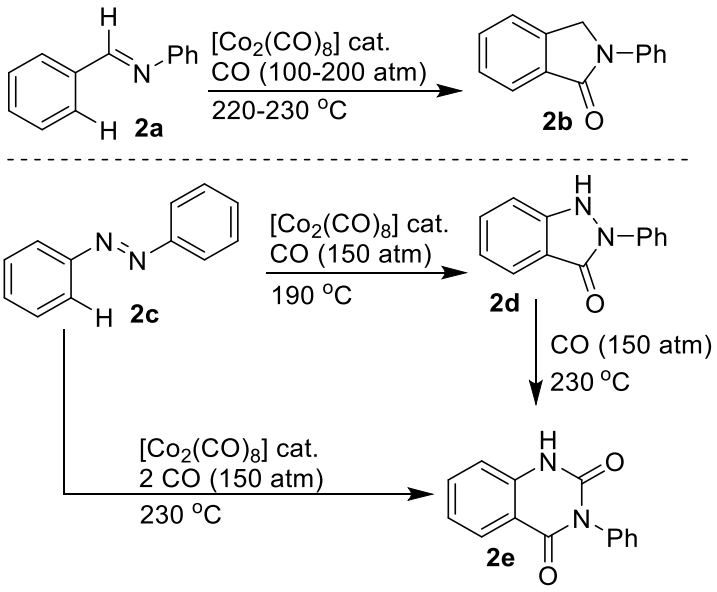
Cross-dehydrogenative coupling (CDC), is a better cross-coupling technique with minimum drawbacks.[2] The pre-functionalization of hydrocarbons into organohalides is not necessary for the direct cross-coupling between two hydrocarbons. However, an oxidant is used to accept the redundant electrons for this reaction. Despite having many benefits, there are also many drawbacks, such as regioselectivity, homocoupling which makes it difficult to selectively activate just one C-H bond due to the abundance of these bonds.

C-H activation and functionalization: C-H activation[3] has been discovered to be the effective method for forming C-C and C-X bonds in recent and it does not require pre-functionalized starting material. It is a process in which unactivated C-H bond gets converted into a reactive substance *via* a transition metal catalyst, which is then transformed into the desired product with the aid of various functional groups (Scheme 1).



Scheme 1: General representation of C-H Activation/Functionalization

To contribute to this new strategy Murahashi's group[4a] came up with insertion of carbon monoxide into *ortho*-C(sp^2)-H bond of aldimine and azobenzene[4b] using Co catalysis (Scheme 2). They have demonstrated that coupling of an aldimine in the presence of [$Co_2(CO)_8$] in the presence of CO atm at elevated temperature led to the insertion of CO into the *ortho*-C(sp^2)-H bonds of aldimine, thereby the formation of isoindolinone scaffolds. Further, the reaction of azobenzene with [$Co_2(CO)_8$] under different equivalents of CO has led to the synthesis of indazolone **2d** and 3-phenyl-2,4-dioxo-1, 2, 3, 4-tetrahydroquinazoline **2e** moiety (Scheme 2).



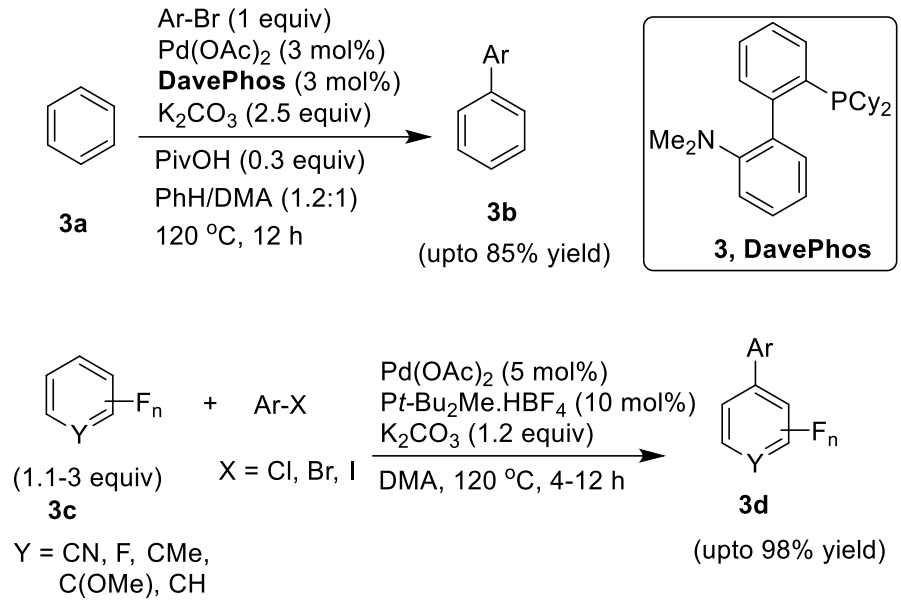
Scheme 2: Cobalt catalyzed *ortho*-carbonylation of C-H bonds

The directed C-H bond activation focuses on mono-dentate and bi-dentate directing group strategy. Herein, a catalyst is brought in close connection to the substrate due to the coordination of directing group with the metal. This step relaxes the site selectivity of C-H bond activation, and directed C-H functionalization is achieved effectively.

C-H activation reactions are generally done in two ways:

(i) Non-directed or direct C-H activation

(ii) Directing group assisted C-H activation.



Scheme 3: Representative example of direct C-H activation

Fagnou's group in 2006[5a] disclosed the direct arylation of benzene using a combination of palladium-pivalic acid as a co-catalyst. The optimized reaction condition involves substrate **3a** (1 equiv), $Pd(OAc)_2$ (3 mol%), DavePhos (3 mol%), K_2CO_3 (2.5 equiv), PivOH (0.3 equiv), aryl halide (1 equiv) in toluene/DMA at 120 °C for 12 h to afford the corresponding arylated product **3b** in good to excellent yield. This method is only limited to the aryl bromide, but aryl chloride and aryl iodide were incompatible (Scheme 3). Following the same concept, Fagnou's group in 2006[5b] reported the direct arylation of electron-deficient polyfluoroarene **3c** with an aryl bromide under palladium-catalyzed conditions. Other than aryl bromides, other aryl halides (Ar-Cl, Ar-I) could also be tolerated under the reaction condition. Tetrafluoro-, trifluoro-, difluoro-, and even fluorobenzene could all be selectively arylated even though they had mono-, di-, and tri-arylation sites. However, this may be minimized by adding an excess amount of fluoroarene (Scheme 3).

The directed C-H activation[6] has become one of the most popularly used techniques because it addresses the issue of regioselectivity by guiding the entering group to a specific position. irected C-H activation is generally done in three ways:

1. **Directing group-assisted C-H functionalization:** In this approach, the directing group linked to the molecule coordinates with the metal complex to produce a metallacycle, which then searches for proximal hydrogen to activate at a remote position *via* a bicyclic metallacycle. However, it requires two extra steps to attach and remove the directing group

thus, this method also has certain limitations. Some of the bidentate directing group from different research groups is shown in figure 1.

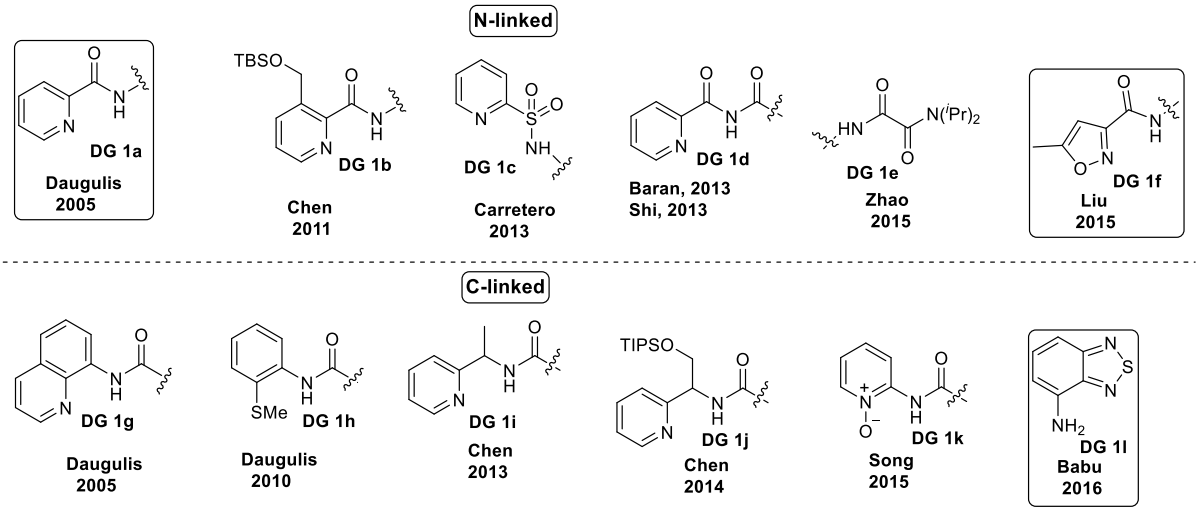
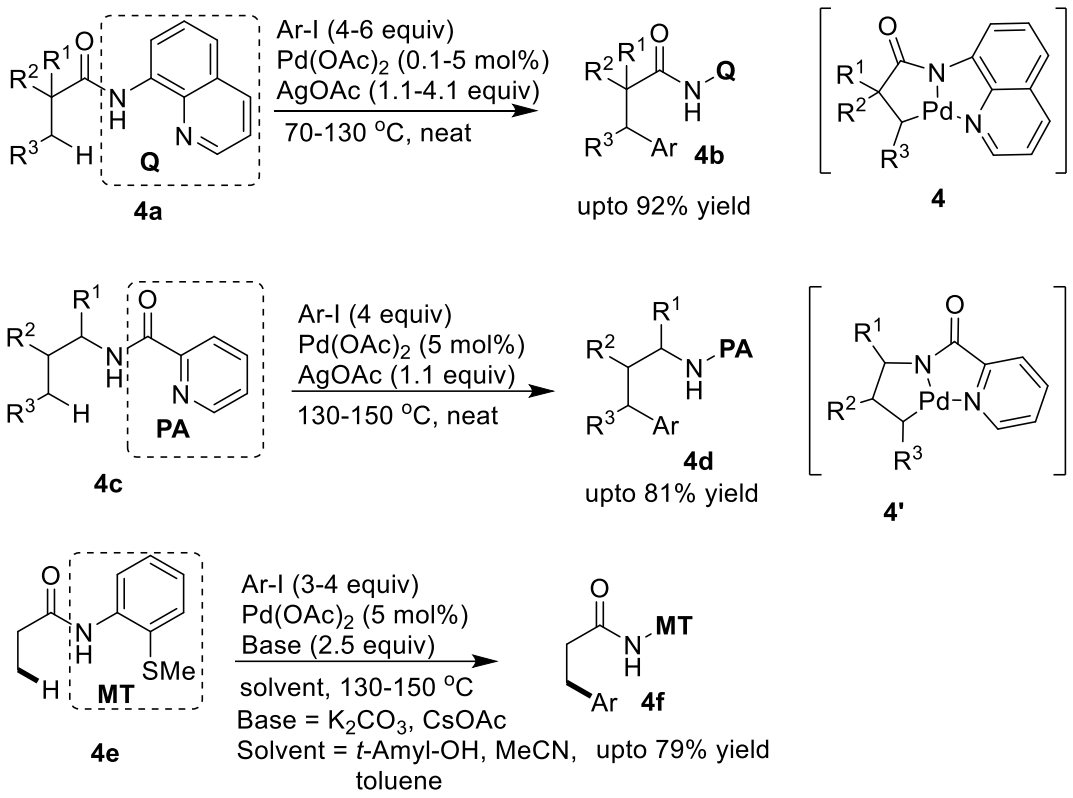


Figure 1: Bidentate DGs used in C-H Functionalization

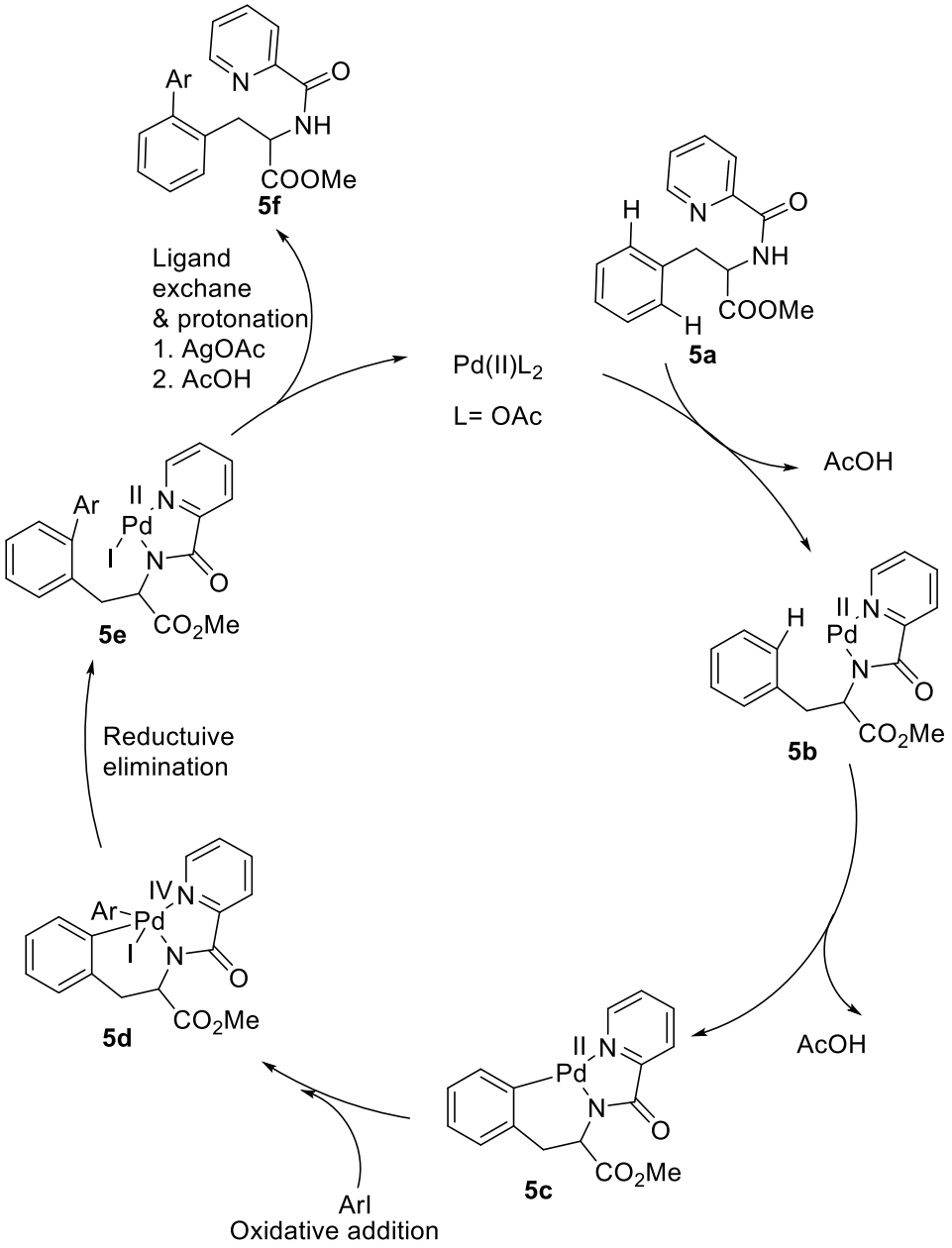
2. **Transient directing group-assisted C-H functionalization:** Despite the significant progress in directing group-assisted C-H activation, its installation, and removal limit its application and efficiency. Transient directing group-assisted C-H activation addresses this issue by in-situ coordination with the functional group of the molecules. Upon C-H activation, subsequent dissociation from the molecules makes this method highly efficient.
3. **Functional group-assisted C-H functionalization:** It is a more advanced technique for achieving site-selective C-H bond functionalization. The native functional group in the molecule act as a directing group, thus eliminating the requirement of the directing group, making the reaction highly efficient and atom economical.

Bidentate directing groups for the C-H functionalization: In 2005[7a] Daugulis group introduced 8-aminoquinoline (8-AQ) and 2-picolinic acid (PA) as a bidentate directing group for C(sp^3)-H arylation of carboxamides. The arylation of primary and more challenging secondary C(sp^3)-H arylation was performed using 8-AQ and PA as an auxiliary (Scheme 4). However, when 8-AQ was employed for β-C(sp^3)-H, arylation, a mixture of mono and bis arylated product was obtained. To address this issue, Daugulis and co-workers in 2010 invented 2-methylthioaniline (MT)[7b] as a bidentate directing group for monoselective arylation. The authors believed that bidentate monoanionic auxiliaries might help in achieving both C-H activation and oxidative addition step by stabilizing putative Pd(IV) intermediates.



Scheme 4: Pd(II)-catalyzed C(sp^3)-H arylation directed by AQ, PA, and MT.

The plausible mechanism of picolinamide-directed regioselective C-H functionalization of *δ*-C(sp^2)-H activation is explained in scheme 5. At first, coordination of **5a** to the $Pd(OAc)_2$ followed by ligand exchange, gives **5b.** Next, the abstraction of most proximal *δ*-H of the phenyl ring generates (5, 6) membered palladacycle intermediate followed by oxidative addition (transfer to Pd(II) to Pd(IV)) of Ar-I, which leads to the formation of **5d** complex. Further ligand exchange followed by reductive elimination gives the desired arylated product **5f** (Scheme 5).

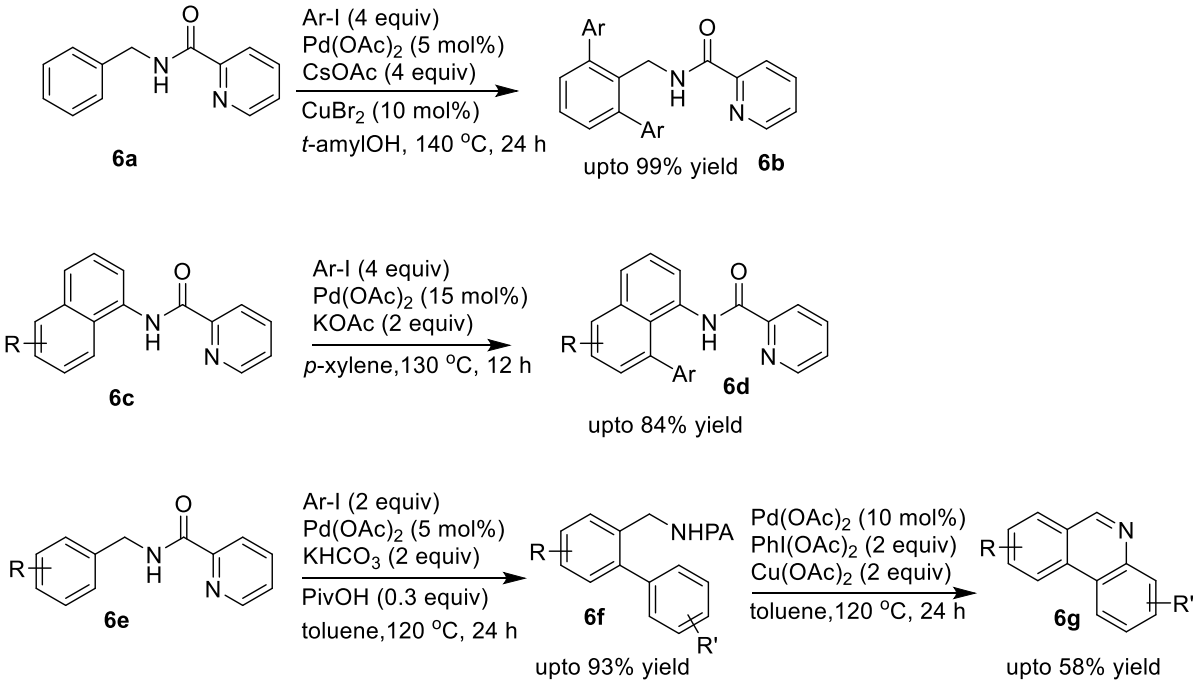


Scheme 5: General mechanism of picolinamide directing group-aided C-H activation reaction.

Given the brief introduction of C-H activation and the related methods, the next section of this chapter will be presented with the literature reports pertaining to picolinamide-aided C-H functionalization reactions, as majority of this thesis work is carried out using picolinamide as the directing group.

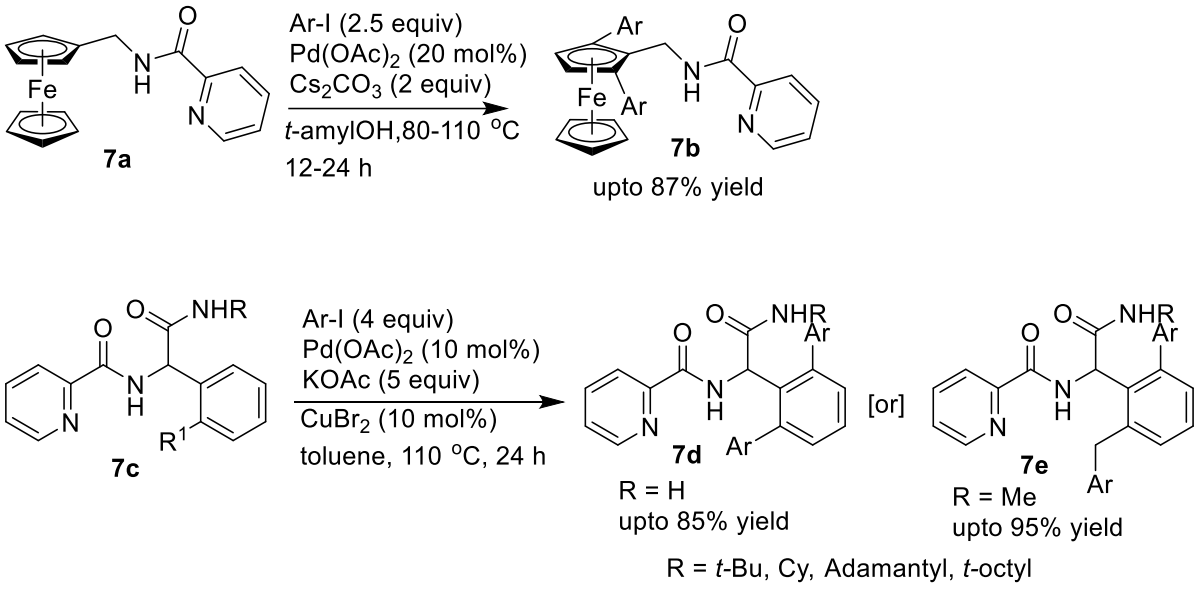
Picolinamide assisted C(sp^2)-H arylation of carboxamide: Daugulis group after the introduction of picolinic acid as a directing group for the arylation C(sp^3)-H bonds. His group further continued to investigate picolinic acid for the arylation of C(sp^2)-H bonds. In this context, they have carried out Pd(II)-catalyzed picolinamide aided C(sp^2)-H arylation of the

benzylamine system[8a] (Scheme 6). Following this concept Qi group in 2013[8b] reported Pd(II)-catalyzed picolinamide aided regioselective C-8 arylation of naphthylamine derivatives. The theoretical calculation reveals that the reaction proceeds *via* a sequential C-H activation/oxidative addition route. The reaction condition utilizes substrate **6c** (1 equiv), $Pd(OAc)_2$ (15 mol%), KOAc (2 equiv) in *p*-xylene at 130 °C for 12 h to give C-H arylated product **6d** (Scheme 6). Chen's group in 2013[8c] synthesized phenanthridines *via* palladium-catalyzed picolinamide-directed sequential C–H functionalization of benzylamine substrates. Under the reaction condition, at first arylation reaction takes place, followed by intramolecular C-H amination reaction with $PhI(OAc)_2$ to accomplish desired dihydrophenanthridine moiety, which further oxidizes with $Cu(OAc)_2$ catalyst to get phenanthridines **6g** (Scheme 6).



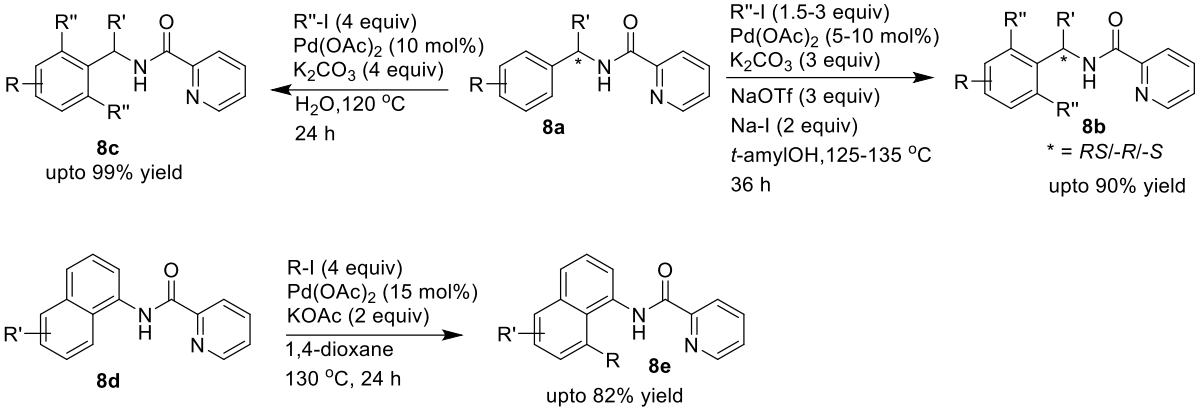
Scheme 6: Picolinamide directed $C(sp^2)$-H functionalization of arylamine carboxamide.

Elias group in 2017[8d] reported C-H arylation/alkylation/allylation of metal (Fe) sandwich compounds *via* picolinamide as a directing group. The optimized reaction condition involves substrate **7a** (1 equiv), $Pd(OAc)_2$ (20 mol%), Cs_2CO_3 (2 equiv), Ar/R-I (2.5 equiv) in *t*-amylOH at 80-110 °C for 12-24 h to give C-H arylated product **7b** (Scheme 7). Garcia's group in 2022[8e] disclosed Pd(II)-catalyzed protocol for the synthesis of *ortho*-diaryl, *ortho*-monoaryl, and *bis*-diarylmethane-glycinamide scaffolds using picolinic acid as a directing group (Scheme 7).



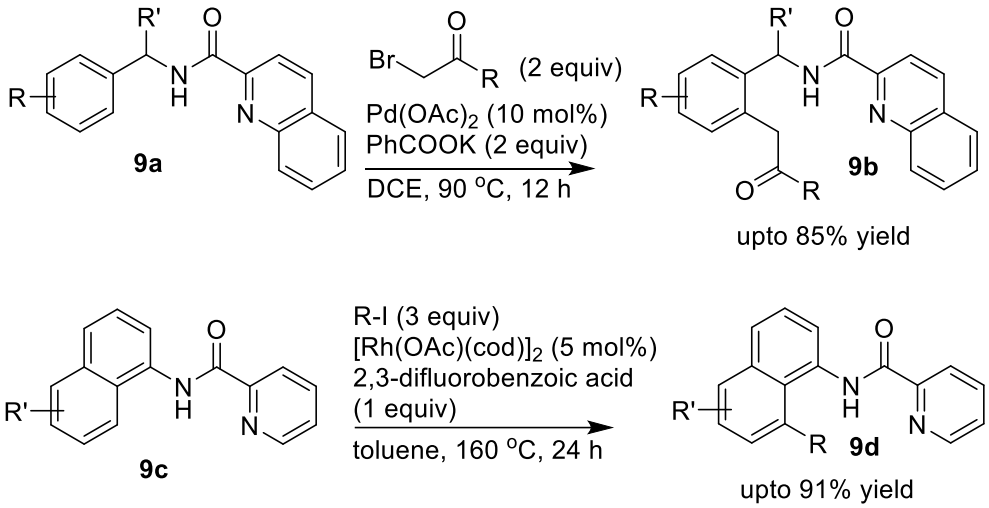
Scheme 7: Picolinamide directed C(sp^2)-H functionalization of ferrocene and aryl-glycinamide carboxamide.

Picolinamide assisted C(sp^2)-H alkylation of carboxamide: Chen group in 2011[9a] reported highly efficient and silver-free protocol for *ortho*-C-H alkylation of racemic and chiral *α*-methylbenzylamine systems. The reaction condition offers high tolerance of alkyl halides as well as benzylamines. The alkylation reaction condition utilizes substrate **8a** (1 equiv), $Pd(OAc)_2$ (5-10 mol%), K_2CO_3 (1.5-2 equiv), NaOTf (3 equiv), NaI (2 equiv, for Cl substrate only) in *t*-amylOH at 125-135 °C for 36 h to give C-H alkylated product **8b**. NaOTf, a non-nucleophilic promoter, is essential for the reaction (Scheme 8). Daugulis and co-workers in 2013[8a] published an article dealing with Pd(II)-catalyzed C-H alkylation reaction of benzylamine/ racemic *α*-methylbenzylamine systems. The reaction protocol utilizes substrate **8a** (1 equiv), $Pd(OAc)_2$ (10 mol%), K_2CO_3 (4 equiv), and R''-I (4 equiv) in water at 120 °C for 24 h to give C-H alkylated product **8c**. Qi *et al.* in 2014[9c] developed highly regioselective Pd(II)-catalyzed alkylation of C8-bonds of naphthylamides *via* picolinamide or quinolinamide as a bidentate directing group. Various C8-alkylated naphthylamides **8e** can be prepared in excellent yields using this protocol. The developed reaction condition has a high tolerance of alky halides (Scheme 8).



Scheme 8: Picolinamide directed C(sp^2)-H alkylation of arylamine carboxamide.

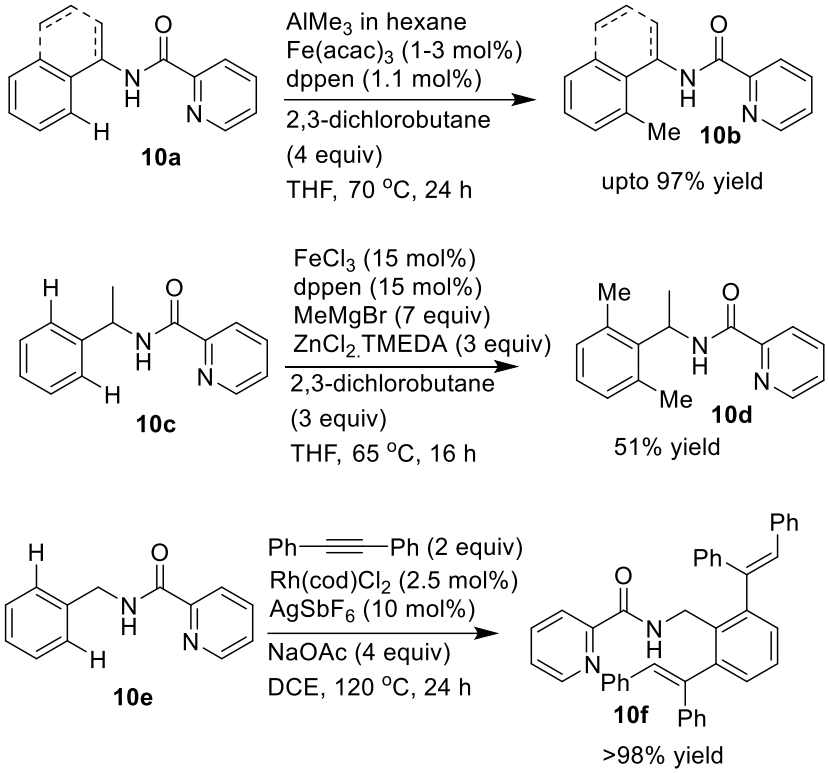
Huang and co-workers in 2016[9c] reported *ortho*-C-H alkylation of benzylamines using *α*-bromo ketones and nitriles, which can be further transformed to 3-aryl isoquinolines *via* hydrolysis of bis C-H alkylated moiety **9b** (Scheme 9). Chatani's group in 2018[10d] reported rhodium-catalyzed alkylation of C8-bonds of naphthylamides using picolinic acid as a directing group to give C8- alkylated naphthylamides **9d**. The reaction protocol applies to alky halides, styrenes, and *α,β*-unsaturated carbonyl compounds (Scheme 9).



Scheme 9: Picolinamide directed C(sp^2)-H alkylation of naphthylamine/benzylamine carboxamide

.**Picolinamide directed C(sp^2)-H methylation and olefination of carboxamide:** Nakamura's group in 2015[10a] developed Fe-catalyzed C-H methylation of naphthylamine using picolinic acid as a directing group. The methylation condition utilizes substrate **10a** (1 equiv), $Fe(acac)_3$ (1-3 mol%), dppen (1.1 mol%), $AlMe_3$ in hexane, 2,3-DCB (4 equiv) in THF at 65 °C for 24 h to form methylated product **10b** in excellent yield (Scheme 10). In 2017[10b], Ackermann and

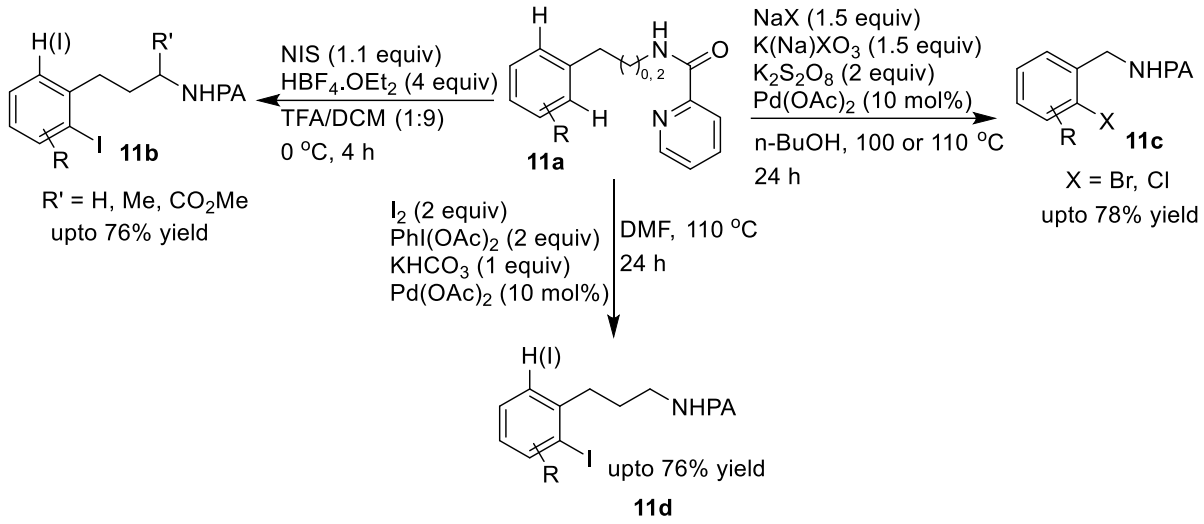
co-workers carried out Fe-catalyzed C-H methylation of α-methylbenzylamine using picolinic acid as a directing group (Scheme 10). In 2015[10c], Carretero's group developed Rhodium(I)-catalyzed site-selective C-H olefination of benzylamine moiety using phenylacetylene as a coupling partner. The authors have also performed mechanistic calculations based on isolating Rh(I)-picolinamide complex, DFT calculation, and deuterium experiments to explain site-selective control (Scheme 10).



Scheme 10: Picolinamide directed C(sp^2)-H methylation and olefination of naphthylamine/benzylamine carboxamide

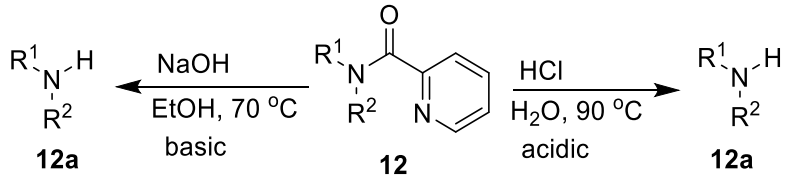
Picolinamide directed C(sp^2)-H halogenation of carboxamide: Chen's group in 2013[11d], reported a versatile and highly efficient palladium-free protocol for remote ε-C-H iodination of phenylpropylamine moiety. *Ortho*-iodinated phenylpropylamine moiety further utilized for the synthesis of various tetrahydroquniolines scaffolds (Scheme 11). Chen and co-workers in 2014[11e], demonstrated Pd(II)-catalyzed, picolinamide-directed NaX promoted C-H halogenation of benzylamine scaffolds. The reaction protocol uses unique combination of K(Na)XO_3 and $K_2S_2O_8$ to achieve *ortho*-C-H halogenated product in good to excellent yields (Scheme 11). Chen's group in 2016[11f], further disclosed a palladium-catalyzed approach for *ortho*-iodination of γ-arylpropylamines. In addition to their previously described PA-directed electrophilic aromatic substitution strategy to this transformation, this reaction proceeds

preferably with a variety of *γ*-arylpropylamines carrying highly electron-donating or withdrawing substituents (Scheme 11).



Scheme 11: Picolinamide directed C(sp^2)-H halogenation of arylamine carboxamide.

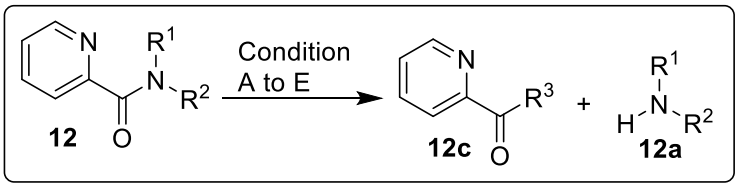
Methods available for removal of picolinyl moiety: Picolinic acid (PA) introduced by Daugulis[7a], is an efficient and powerful directing group for regioselective C-H bond functionalization of amine-based substrates. Numerous methods are available for the coupling of picolinyl group with amine substrates with the help of an activator (HATU, TBTU, EDCI, HOBt, and $EtCO_2Cl$).[9a, 11a, 11b, 11c, 11d, 11e] A directing group must be removable from the substrate after C-H functionalization for further synthetic utilities.



Scheme 12: Removal of picolinyl group under acidic and basic conditions.

The most fundamental approach for the removal of the PA group is acidic[12b] and basic[12a] hydrolysis under optimum reaction conditions (Scheme 12). However, harsh conditions often lead to the issue of functional group incompatibility. In 2015[12c], You's group reported $BF_3.OEt_2$ mediated deprotection of picolinamide group, nevertheless being a harsh Lewis acid, has limited its application (Scheme 13). Later on, the removal of the picolinamide group was performed using other Lewis acids, such as $AlCl_3$ (Balaraman)[12d] (Scheme 13). During further development, reductive acidic cleavage (Zn, HCl) was developed by Maulide[12e], Carretero[12f], and Spring[12g] groups (Scheme 13). Daugulis group carried out the removal of the tertiary

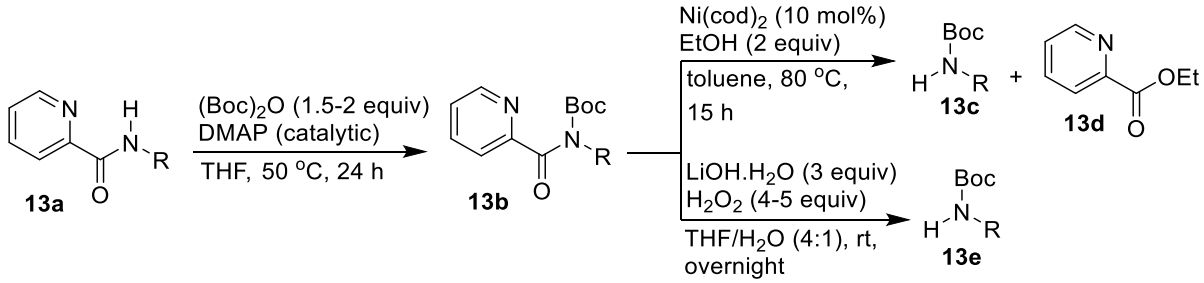
picolinamide group using $LiEt_3BH$[11b] (Scheme 13). Shi's group[12h] treated PCl_5/2, 4-lutidine in MeOH to get corresponding imino ether *via* the formation of an imidoyl chloride intermediate followed by aqueous workup, resulted in the formation of free amine (Scheme 13).



A) $BF_3.Et_2O$ (10 equiv), EtOH, 140 °C, 32 h
B) Zn (15 equiv), $Zn(OTf)_2$ (1 equiv), HCl, H_2O/THF, rt, 1.5-16 h
C) $AlCl_3$ (1 equiv), $^nBuNH_2$ (excess), toluene, 90 °C, 24 h
D) $LiEt_3BH$ (4 equiv), THF, rt, 1 h
E) (i)PCl_5 (2 equiv), 2,4-lutidine (3 equiv), DCM, 70 °C
(ii) MeOH, 0 °C to rt, overnight
(iii) H_2O, rt, 1 h

Scheme 13: Removal of picolinyl group under Lewis acid mediated conditions.

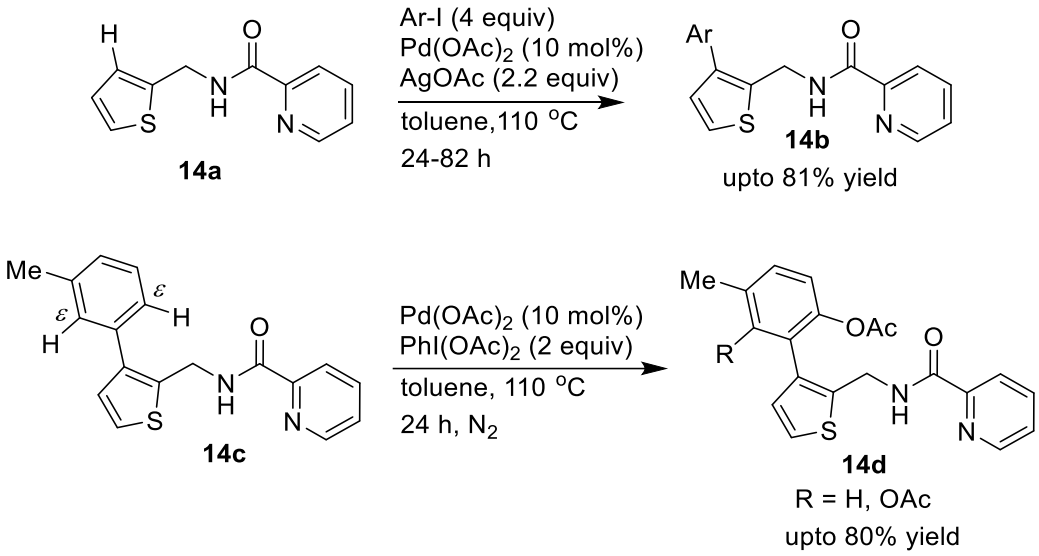
Chen's group in 2011[9a], disclosed a method that involved the activation of the N-H bond *via* Boc protection, which was further hydrolyzed under mild reaction conditions ($LiOH.H_2O/H_2O_2$) to give **13e** (Scheme 14). Maes's group in 2019[12i], revealed a similar but modified version of picolinamide removal where Boc protection followed by $Ni(cod)_2$ mediated cleavage of picolinamide **13c** in excellent yields. In addition, authors have also shown the recycling of ethyl-2-picolinate **13d** (Scheme 14).



Scheme 14: Removal of picolinyl group using Boc protection.

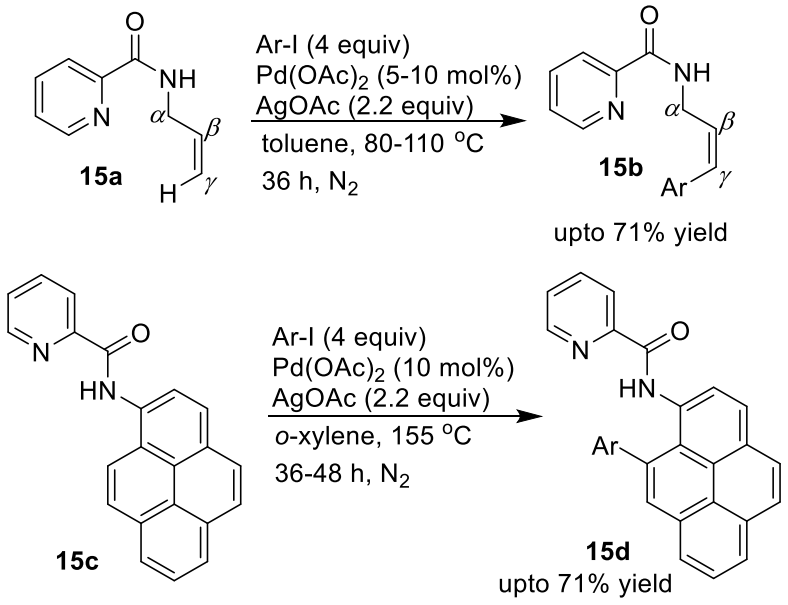
Our group has been involved in the palladium-catalyzed C-H activation of numerous biologically significant scaffolds over a decade using picolinamide as a bidentate directing group. In this context, our group in 2016[13a], revealed Pd(II)-promoted regioselective C-H arylation of C-3 position of 2- or 3-(aminoalkyl)-thiophene and furfurylamine motifs **14a** (Scheme 15). This reaction protocol works well with various aryl and heteroaryl iodides

(Scheme 15). In 2016[13b], we reported Pd(II)-catalyzed remote ε-C-H chemoselective acetoxylation using heteroaryl-aryl-based biaryl systems. We have screened different bidentate directing groups, out of which picolinic acid and pyrazine carboxylic acid were found to be suitable for acetoxylation over oxalyl amide as a directing group (Scheme 15).



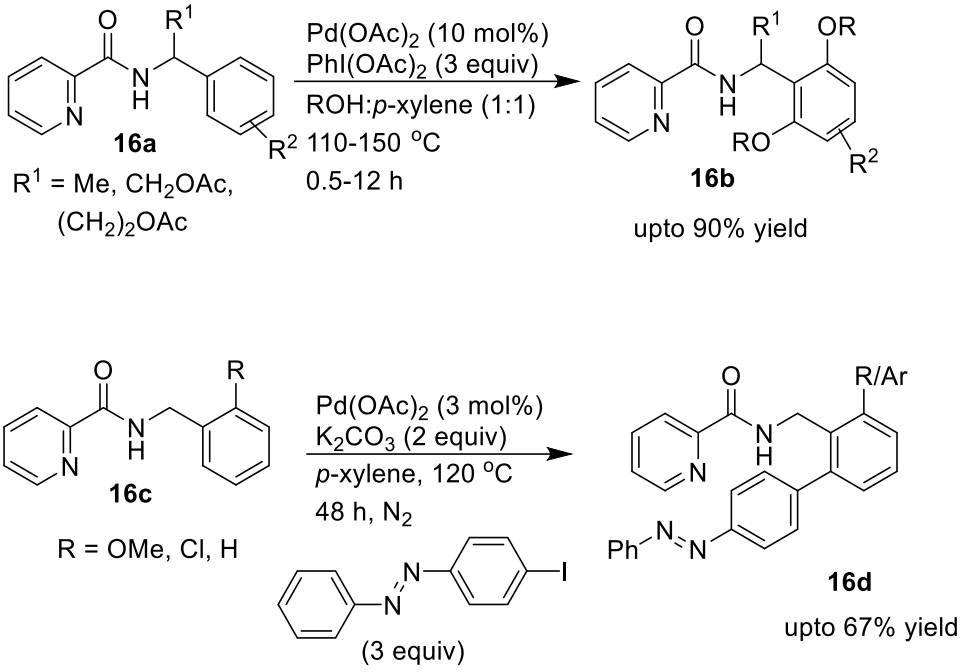
Scheme 15: Picolinamide directed C(sp^2)-H arylation/acetoxylation of hetero-carboxamide

In 2017[13c], we carried out regioselective γ-C-H arylation of allyl amine moiety leading to the formation of Z- cinnamylamine **15b** (E/Z: 2:98) (Scheme 16). Later in the year 2021[13d], we have shown the synthesis of various C1, C10-diarylated pyrene motifs **15d** *via* Pd(II)-catalyzed C-H arylation using picolinic acid as DG (Scheme 16).



Scheme 16: Picolinamide directed C(sp^2)-H arylation of allylamine/pyrene carboxamide

We have also explored picolinamide directed C-H functionalization of benzylamine type systems where in 2022[13e], we disclosed γ-C(sp^2)-H alkoxylation of various α-alkylbenzylamines using alcohols. The reaction protocol was applied to various substrates (α-methylbenzylamines, phenylglycinol, 3-amino-3-phenylpropanol) as well as a wide range of alcohols (Scheme 17). We have also demonstrated the synthesis of azoarene containing benzylamine using picolinic acid as DG[13f] (Scheme 17).



Scheme 17: Picolinamide directed C(sp^2)-H functionalization of benzylamines.

Amino alcohols are a vital class of molecule in chemical synthesis and drug discovery due to their two highly reactive functionalities—amine and alcohol groups that are available for binding to other diverse functional groups. The 1, 2-amino alcohol structural unit is essential to synthesize chiral auxiliaries, ligands, and natural products.[14a,b] Amino alcohols can be broadly classified as vicinal amino alcohols or beta, gamma, and delta amino alcohols. Their application depends upon distance and the stereochemistry between the two functionalities. Various naturally occurring amino alcohols are used as aminopeptidase inhibitor, multi-drug resistance (MDR) inhibitor.

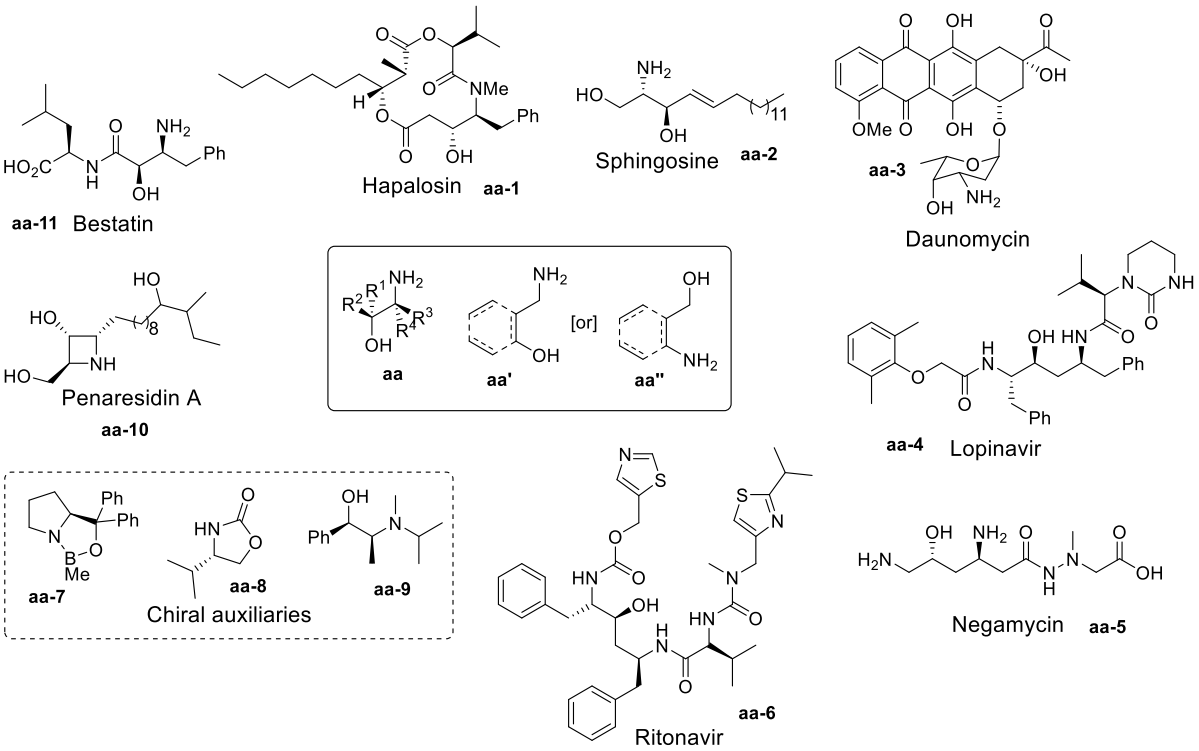


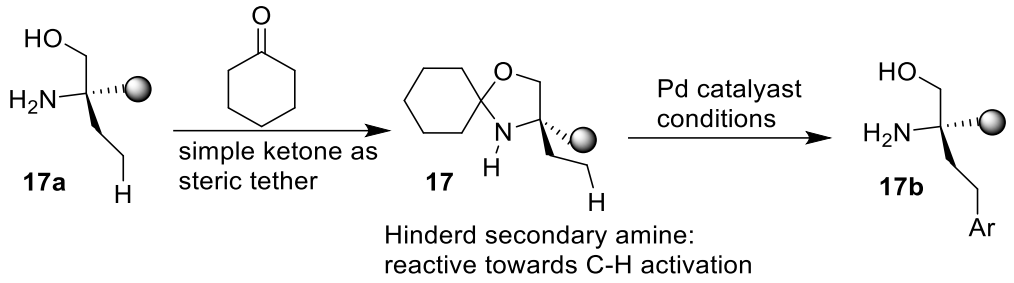
Figure 2: Biologically/Chemically important 1, 2, and 1, 3-amino alcohols

Amino alcohols are most frequently utilized as chiral auxiliaries for enantioselective processes; Evans' "chiral auxiliaries"[15a] are the best-known example. The oxazolidinone moiety has been used in the asymmetric reduction of carbonyl compounds[15c] and the catalysis of aldol and Diels Alder processes. 1,3-amino alcohol core is found in numerous drug and bio active, pharmaceutical molecules[16a], Lopinavir[6b], Ritonavir[16c], and Negamycin[16d] are the small drug molecule containing aliphatic 1,3-amino alcohol core moiety responsible for their bio activity (Figure 2).

Therefore, modifying the structure of the amino alcohol and making the library of various functionalized amino alcohols *via* palladium-catalyzed C-H activation would be of great interest.

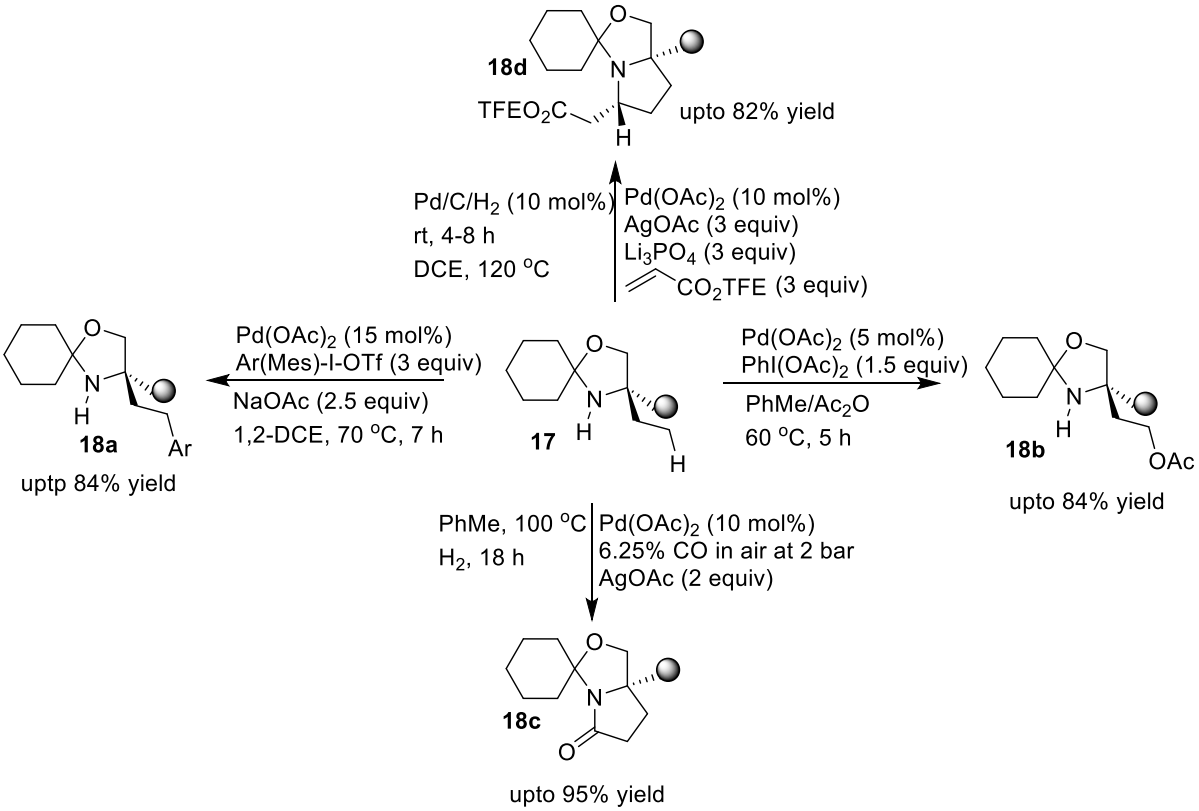
Literature reports dealing with C-H activation/functionalization of amino alcohols:

Gaunt and co-workers in 2015[17] demonstrated the C-H functionalization of primary amino alcohol using a hindered secondary amine which are capable of undergoing sterically promoted C-H activation reaction. The reaction protocol transforms variety of amino alcohols into highly substituted, functionalized biologically important molecules (Scheme 18).



Scheme 18: Schematic diagram of C-H activation of hindered secondary amine

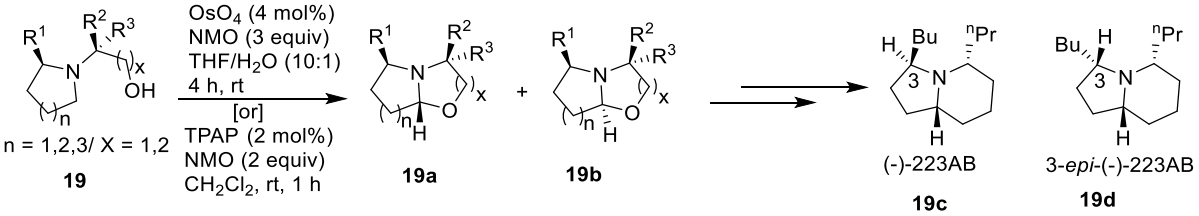
For C-H arylation of the protected amino alcohol, the optimized reaction condition involves substrate **17** (1 equiv), $Pd(OAc)_2$ (15 mol%), Ar(Mes)-I-OTf (3 equiv), NaOAc (2.5 equiv) in 1,2-DCE as a solvent at 70 ^oC for 7 h to afford corresponding C-H arylated product **18a** in good to excellent yield. Authors have further extended the scope of C-H functionalization by successfully attempting C-H acetoxylation (**18b**), carbonylation (**18c**), and alkenylation (**18d**) under optimum reaction conditions (Scheme 19).



Scheme 19: Pd(II) catalyzed C-H activation of amino alcohols

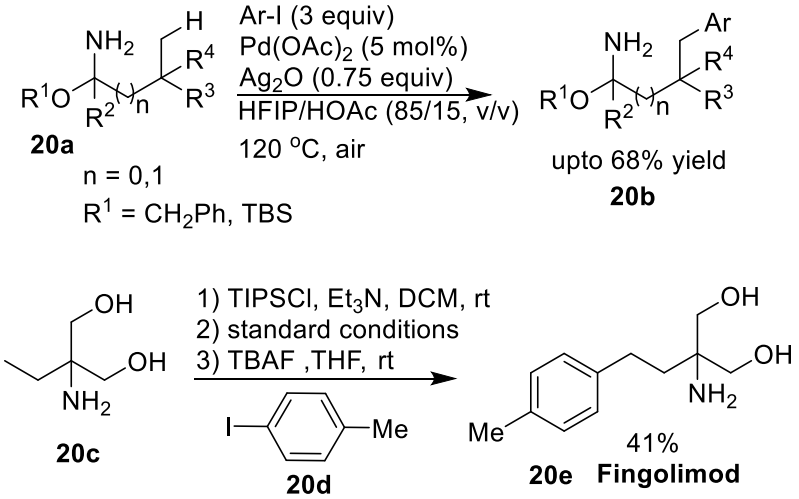
Li and co-workers in 2020[18] demonstrated OsO_4/NMO or TPAP/NMO promoted oxidative cyclization of amino alcohol to access *N, O*-acetal moiety *via* trapping the resulting iminium ion by the attached alcohol group. This transformation was further elaborated to synthesize indolizidines (-)-223AB (**19c**) and 3-*epi*-(-)-223AB (**19d**). The reaction condition involves

substrate **19** (1 equiv), OsO_4 (4 mol%), NMO (3 equiv) in THF/H_2O at rt for 4 h to furnish cyclized product **19a**, **19b** in good to excellent yield. The same transformation is also possible by using TPAP (2 mol%), and NMO (2 equiv) in DCM at rt for 1 h to facilitate the product in excellent yield (Scheme 20).



Scheme 20: Cyclization of amino alcohol to access *N,O*-ketal moiety

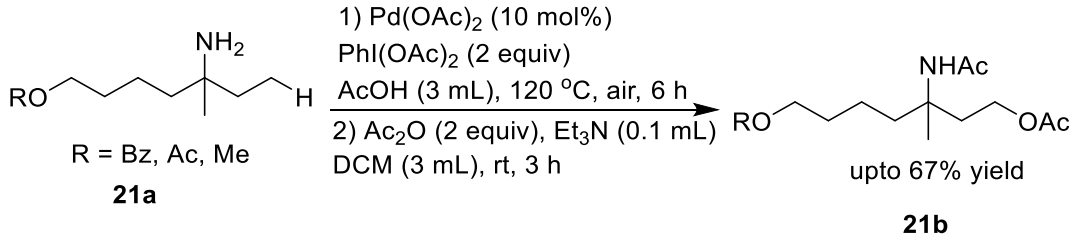
In 2019[19], Yao's group revealed straightforward, simple amine-directed C(sp^3)-H arylation of amines and amino alcohols. The authors also performed the gram-scale synthesis and synthesized a Fingolimod analogue **20e** as part of the method's application. The optimized reaction involves substrate **20a** (1 equiv), $Pd(OAc)_2$ (5 mol%), Ag_2O (0.75 equiv), Ar-I (3 equiv) in HFIP/AcOH (85/15, v/v) as a solvent at 120 ^oC for 24 h under air to form the corresponding product **20b** in good to excellent yield (Scheme 21).



Scheme 21: Amine-directed arylation of amino alcohols

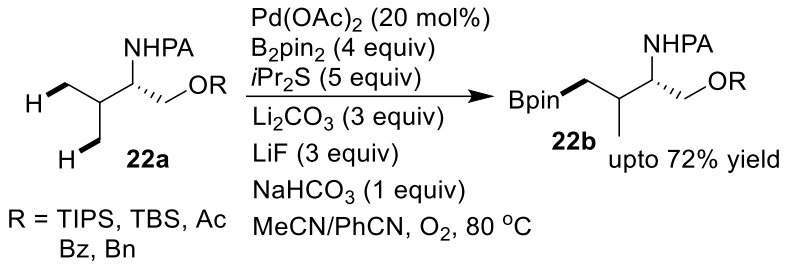
In 2017[20], Shi's group utilized a protonation strategy to synthesize acetoxylated primary amino alcohol *via* palladium-catalyzed C-H activation. This method offers C-H acetoxylated products in a reasonable chemoselective and regioselective manner. The optimal reaction condition for this transformation requires **21a** (1 equiv), $Pd(OAc)_2$ (10 mol%), $PhI(OAc)_2$ (2

equiv) in AcOH (3 mL) as a solvent at 120 °C for 6 h under air to form the corresponding acetoxylated product in good to excellent yield. For ease of isolation, the free amine group was further acetylated using the condition Ac_2O (2 equiv), Et_3N (0.1 mL), in DCM as a solvent at rt for 3 h to furnish *N*-acetylated product **21b** (Scheme 22).



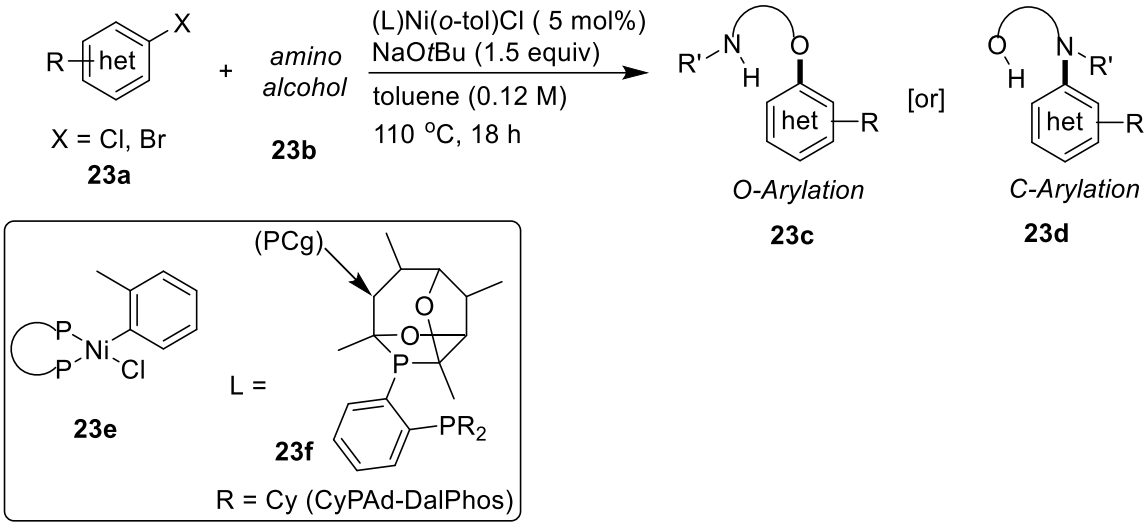
Scheme 22: Amine-directed acetoxylation of amino alcohols

Shi's group in 2014[21] reported palladium-catalyzed picolinamide aided borylation of aliphatic C-H bonds. The borylated product was obtained with good diastereoselectivity, which was determined by proton NMR spectroscopy. The borylation reaction condition involves substrates **22a** (1 equiv), $Pd(OAc)_2$ (20 mol%), B_2pin_2 (4 equiv), *i*Pr_2S (5 equiv), Li_2CO_3 (3 equiv), LiF (3 equiv), $NaHCO_3$ (1 equiv) in MeCN/PhCN as a solvent at 80 °C for 12 h in oxygen atm to give the borylated amino alcohol **22b** (Scheme 23).



Scheme 23: Picolinamide directed borylation of amino alcohols.

In 2023[22], Stradiotto's group developed a method for Nickel-catalyzed chemo-selective *O*- and *N*-arylation of amino alcohols with heteroaryl chloride as an electrophile without any protection of amino alcohols. While selective *N*-arylation was seen in substrates with less-hindered linear alkylamine and aniline groups, CyPAd-DalPhos precatalyst C2 enabled particularly difficult *O*-arylation chemoselectivity in amino alcohols featuring branched primary and secondary alkylamine groups. The arylation reaction to furnish chemoselectivity contains amino alcohol **23b** (1 equiv), heteroaryl chloride **23a** (1.2 equiv), (L)Ni(*o*-tol)Cl (5 mol%), NaO*t*Bu (1.5 equiv) in toluene (0.12 M) as a solvent at 110 °C for 18 h to obtain the corresponding *O*- and *C*-arylated product **23c** or **23d** (Scheme 24).



Scheme 24: Nickel catalyzed O- and N-arylation of amino alcohols.

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Chapter 2

Pd(II)-catalyzed picolinamide-aided γ-C(sp^2)-H functionalization of α-methylbenzylamine and phenylglycinol scaffolds

For the purpose of this thesis work, the work of chapter 2 is adapted with permission from the **publishers**; Bisht, N.[#]; Singh, P. [#]; Babu, S. A.[*] *Synthesis* **2022**, *54*, 4059-4094**.** Title: Pd(II)-catalyzed, picolinamide-aided γ-(sp^2)-C-H functionalization of racemic and enantiopure α-methylbenzylamine and phenylglycinol scaffolds. Singh, P.; Babu, S. A.[*]; Aggarwal, Y.; Patel, P. *Asian J. Org. Chem.* **2021**, *10*, 180-185. Title: Pd(II)-catalyzed picolinamide-aided sp^2 γ- C-H functionalization of phenylglycinol: access to γ- C-H arylated, alkylated and halogenated phenylglycinol scaffolds (# = author contributed equally)

From the last decade of the 20th century, we have witnessed rapid developments in the transition metal-catalyzed C-H activation and functionalization of organic compounds.[1-4] The regio- or site-selective functionalization of organic molecules has been achieved by using the directing group-aided (chelation-assisted) C-H activation/functionalization protocol.[1-4] In particular, the Pd(II)-catalyzed bidentate directing group-aided functionalization (e.g., arylation, alkylation, halogenation, amidation, oxygenation, etc.) is emerging as a valuable method in organic synthesis.[4] Attempt to elaborate the substrate scope in the bidentate directing group-aided site-selective C–H functionalization has been a persistent objective.[4-12]

In continuation to our interest in expanding substrate scope in the directing group-aided C-H functionalization,[8] we become interested in expanding the library of the enantiopure α-methylbenzylamine and phenylglycinol scaffolds *via* the DG-aided sp^2 -γ-C-H functionalization. A literature survey revealed that there exist a limited number of reports dealing with the Pd(II)-catalyzed directing group-aided functionalization of α-methylbenzylamine and aromatic amino alcohol such as phenylglycinol (Scheme 1a and 1b).

The α-methylbenzylamine and phenylglycinol scaffolds are important molecules in organic synthesis and medicinal chemistry.[13-15] Various α-methylbenzylamines and phenylglycinols are used as versatile ligands, chiral auxiliaries and building blocks in synthesizing natural products and bio-active/drug molecules. As depicted in figure 1 *ortho*-C-H-arylated and *N*-modified α-methylbenzylamines are found to exhibit bio-active properties such as a fumaric acid adduct which is widely used for *ih* ion channel modulators for use in psychotherapeutics **2d**, calcium receptor modulator **2a**, HCl adduct**,** anacetrapib **2e** is a CETP inhibitor which is used to treat elevated cholesterol level. Phenylglycinols are known to be found in prevalent

bio-active molecules such as factor Xa inhibitor **2g**, protein kinase C modulator **2c**, EGFR inhibitor **2l** (Figure 1).[13-15]

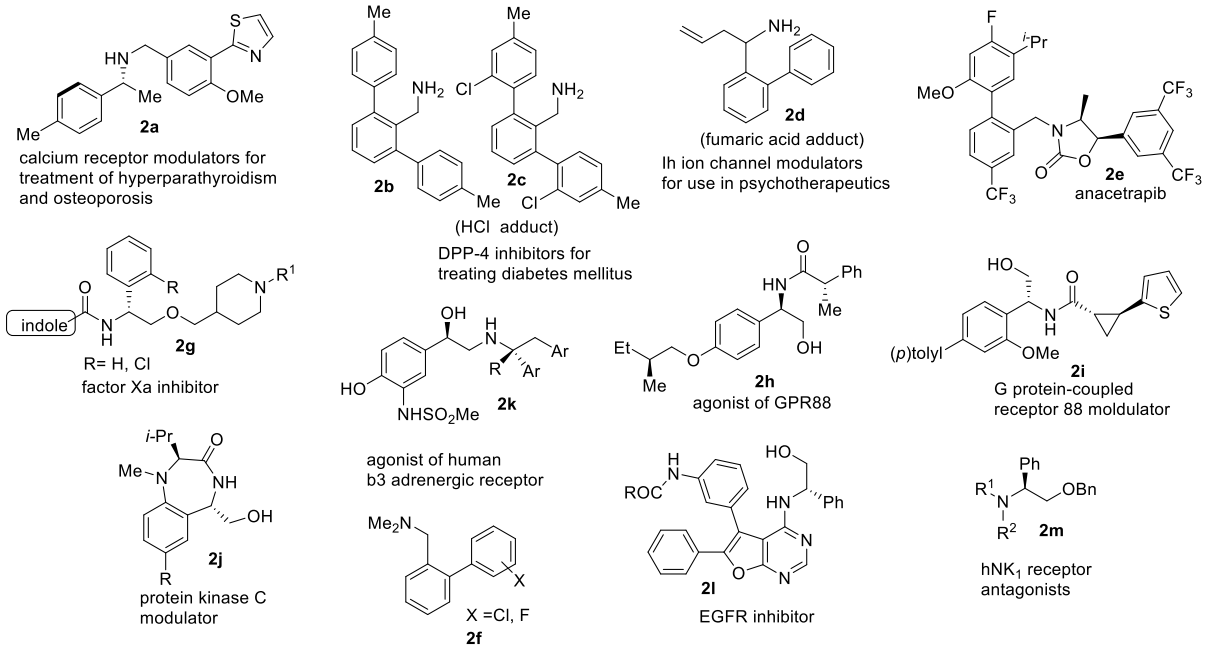
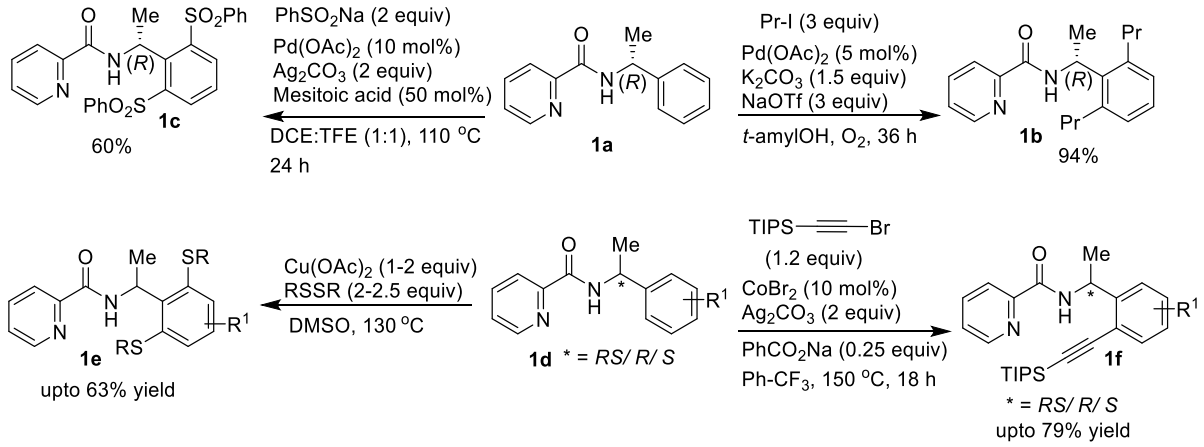


Figure 1: Examples of bio-active *α*-methylbenzylamines and phenylglycinols scaffolds.

Encouraged by the importance of *α*-methybenzylamine and phenylglycinol and the efficiency of the C-H activation strategy, we intended to modify *α*-methybenzylamine and phenylglycinol *via* an efficient and step economical C-H functionalization strategy. In this context, in the next section, we present some of the available literature reports for α-methybenzylamine and phenylglycinol *via* C-H functionalization route.

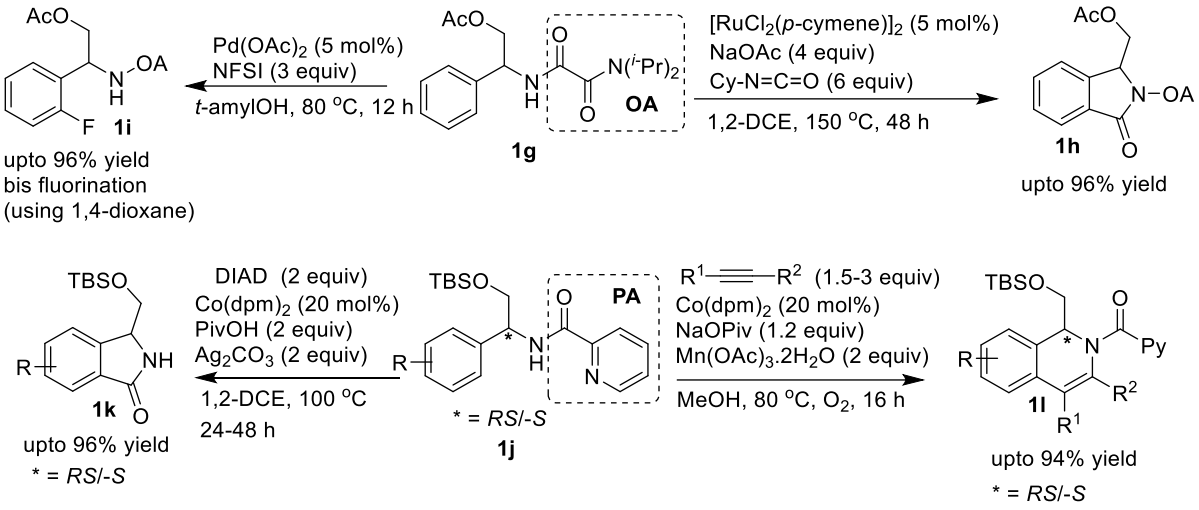
Some selected literature reports dealing with C-H functionalization of *α*-methylbenzylamines: Chen group in 2011[11b] reported a highly efficient and silver-free protocol for *ortho*-C-H alkylation of chiral *α*-methybenzylamine system. The alkylation reaction condition utilizes substrate **1a** (1 equiv) $Pd(OAc)_2$ (5 mol%), K_2CO_3 (2 equiv), NaOTf (3 equiv) in *t*-amylOH at 125-135 ^oC for 36 h to give C-H alkylated product **1b** (Scheme 1a). Daugulis and co-workers in 2012[9c] revealed copper promoted highly efficient sulfenylation of the benzylamine system. The use of inexpensive copper acetate and a removable directing group are important features that increase the reaction's applicability. The reaction exhibits excellent *ortho*-C-H bond selectivity, high generality, and substantial functional group tolerance (Scheme 1a).



Scheme 1a: Representative examples for C-H functionalization of *α*-methylbenzylamines

Balaraman's group in 2016[11a] reported cobalt-catalyzed C-H alkynylation of racemic and enantiopure benzylamines. The optimized reaction condition involves the reaction of substrate **1d** (1 equiv), (triisopropylsilyl)ethynyl bromide (1.2 equiv), $CoBr_2$ (10 mol%), Ag_2CO_3 (2 equiv), $PhCO_2Na$ (0.25 equiv) in trifluoro solvent was heated at 150 °C for 18 h to furnish corresponding alkynylated product **1f** in good to excellent yield having good range of substrate selectivity (Scheme 1a). Later Samanta's group in 2019[11c] reported a Pd(II)-catalyzed simple and straightforward approach for regioselective sulfonylation of chiral *α*-methybenzylamine with sodium sulfonate. Additionally, the authors carried out control experiments and confirmed that the reaction follows a radical pathway (Scheme 1a).

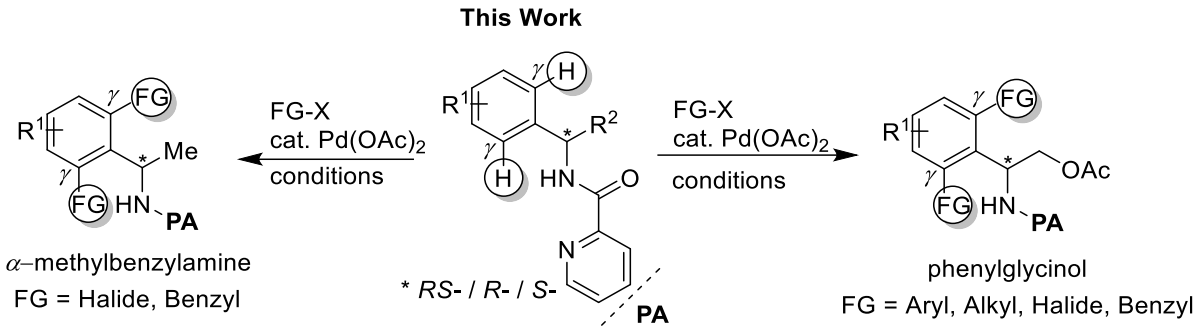
Some selected literature reports related to C-H functionalization of phenylglycinols: Zhao's group in 2015[9g] reported Pd(II)-catalyzed oxalylamide-directed mono and bis C-H fluorination of phenylglycinol. The cheap *N*-fluorobenzenesulfonamide is used as a source of [F^+]. Authors have also modified the selective mono and bis C-H fluorination condition by changing the solvent from *t*-amylOH to 1, 4-dioxane (Scheme 1b). Shi's group in 2017[9i] revealed the synthesis of isoindolin-1-ones *via* Ruthenium-catalyzed intramolecular C-H carbonylation. This protocol exhibits tolerance to various benzylamines with moderate to excellent yields. The optimized reaction condition involves substrate **1g** (1 equiv), $[RuCl_2(p\text{-cymene})]_2$ (5 mol%), NaOAc (4 equiv), Cy-N=C=O (6 equiv) in 1,2-DCE as a solvent at 150 °C for 48 h to give corresponding C-H carbonylated product **1h** (Scheme 1b).



Scheme 1b: Representative examples for C-H functionalization of phenylglycinol

During our involvement in the picolinamide DG-aided *ortho* C-H functionalization of enantiopure *α*-methylbenzylamine and phenylglycinol scaffolds, Grigorjeva and co-workers in 2020[9j] reported an efficient and highly regioselective method for the synthesis of 1-hydroxymethyltetrahydroisoquinolines **1l** *via* Co(II)-catalyzed C-H functionalization of phenylglycinol with alkynes. This reaction method works well with internal and terminal alkynes and offers high functional group tolerance (Scheme 1b). Grigorjeva group in the same year[10c] disclosed the synthesis of 3-hydroxymethylisoindolinones **1k** *via* Co(II)-catalyzed C-H functionalization of phenylglycinol. The developed reaction protocol works well with a wide range of substrate scope and excellent regioselectivity with retention of stereochemistry (Scheme 1b). Consequently, we disclosed[12b] our preliminary works on the palladium(II)-catalyzed picolinamide-aided sp^2 *γ*-C-H functionalization of phenylglycinols.

The available reports revealed limited investigations on the sp^2 γ-C-H functionalization of enantiopure α-methylbenzylamine and phenylglycinol scaffolds (Scheme 1a and 1b). Apart from the attempts and examples that have been shown in Scheme 1a and 1b, to the best of our knowledge, there exists no literature precedent for the Pd(II)-catalyzed picolinamide DG-aided arylation, benzylation, and halogenation of *ortho* C-H bonds of enantiopure *α*-methylbenzylamine and phenylglycinol scaffolds.[4-12] Accordingly, we started our investigation to expand the library of enantiopure *α*-methylbenzylamine and phenylglycinol scaffolds *via* the picolinamide DG-aided sp^2 *γ*-C-H functionalization.

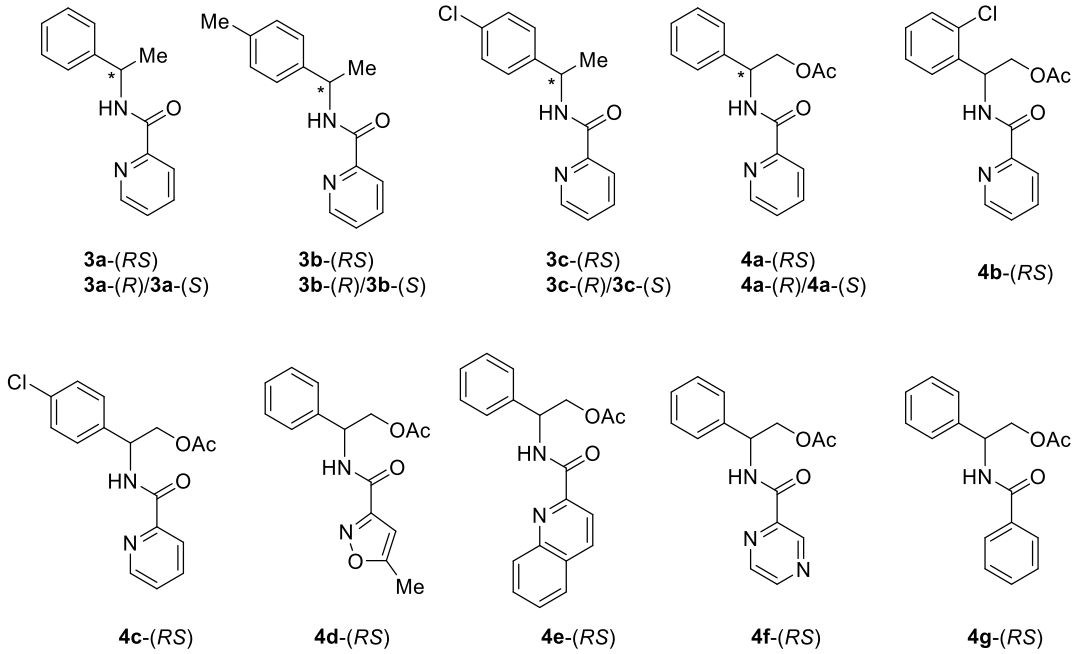


Scheme 2: Theme of the work

We herein report our efforts toward expanding the library of both racemic and enantiopure *α*-methylbenzylamine and phenylglycinol scaffolds *via* the DG-aided sp^2 *γ*-C-H functionalization (Scheme 2).

Result and discussion:

To begin with our investigations on the Pd(II)-catalyzed, directing group-aided sp^2 *γ*-C-H functionalization of *α*-methylbenzylamine and phenylglycinol scaffolds, initially we prepared suitable DG-linked *α*-methylbenzylamine- and phenylglycinol-based substrates (Scheme 3). Accordingly, various racemic *α*-methylbenzylamines and phenylglycinols were linked with 2-picolinic acid (PA) to afford the racemic *α*-methylbenzylamine and phenylglycinol substrates **3a-c**-(*RS*) and **4a-c**-(*RS*) possessing picolinamide DG.

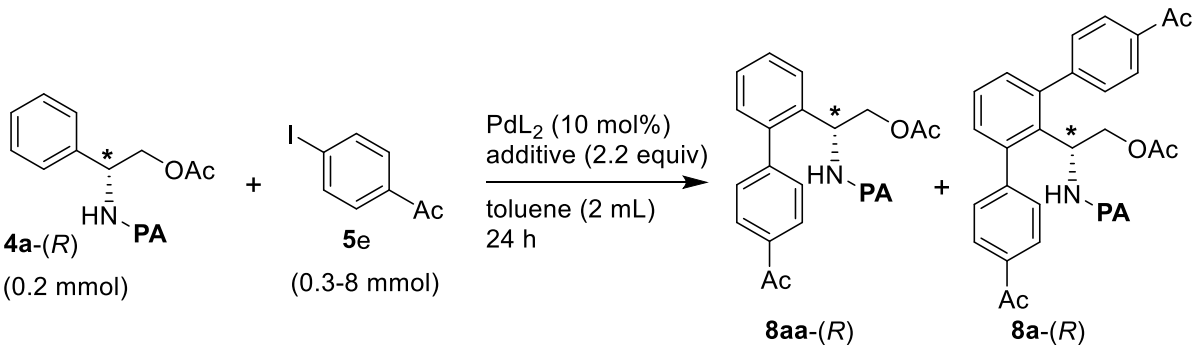


Scheme 3: Preparation of racemic and enantiopure α-methylbenzylamine and phenylglycinol linked with different directing groups.

Phenylglycinol was linked with 5-methylisoxazole-3-carboxylic acid (MICA), pyrazine-2-carboxylic acid, quinoline-2-carboxylic acid, and benzoic acid to afford the corresponding **4d-g**-(*RS*). Subsequently, enantiopure (*R*) and (*S*) α-methylbenzylamines were linked with 2-picolinic acid to afford the corresponding enantiopure α-methylbenzylamine substrates **3a-c**-(*R*) and **3a-c**-(S). Furthermore, (*R*) and (*S*) phenylglycinols were linked with 2-picolinic acid to afford the corresponding enantiopure phenylglycinol substrates **4a**-(*R*) and **4a**-(*S*).

Initially, we optimised reaction conditions to find suitable reaction conditions that will afford enantiopure γ-C(sp^2)-H arylated phenylglycinol derivative. In this regard, we carried out the picolinamide-aided arylation of enantiopure phenylglycinol substrate **4a**-(*R*) (0.2 mmol) with aryl iodide **5e** (1.5 equiv) in the presence of the $Pd(OAc)_2$ catalyst (10 mol%) and AgOAc as an additive (iodide ion scavenger)[4,5b,g] in toluene at 110 ^oC for 24 h. This reaction was found to yield the bis γ-C(sp^2)-H arylated phenylglycinol derivative **8a**-(*R*) in 60% yield and the mono γ-C(sp^2)-H arylated phenylglycinol derivative **8aa**-(*R*) in 7% yield. Then, we performed the same reaction by using 5 mol% of the $Pd(OAc)_2$ catalyst, which afforded the bis γ-C(sp^2)-H arylated phenylglycinol derivative **8a**-(*R*) in 16% yield (entries 1 and 2, Table 1). Next, we performed the Pd(II)-catalyzed *ortho* C-H arylation of enantiopure substrate **4a**-(*R*) by using some additional additives or different iodide ion scavenging additives instead of AgOAc and various Pd catalysts. Accordingly, the entries 3-16 of Table 1 show the attempts which yielded the bis γ-C(sp^2)-H arylated phenylglycinol derivative **8a**-(*R*) in 0-56% yields and the mono γ-C(sp^2)-H arylated phenylglycinol derivative **8aa**-(*R*) in 0-41% yields, respectively. Notably, the reaction involving KOAc as an additive yielded the mono γ-C(sp^2)-H arylated phenylglycinol derivative **8aa**-(*R*) in a maximum of 41% yield (entry 16, Table 1). The Pd(II)-catalyzed *ortho* C-H arylation of enantiopure substrate **4a**-(*R*) in *t*-AmylOH or 1,4-dioxane solvent afforded the products **8aa**-(*R*)/**8a**-(*R*) in low yields (entries 17 and 18, Table 1). Next, we performed the Pd(II)-catalyzed, AgOAc-promoted *ortho* C-H arylation of enantiopure substrate **4a**-(*R*) with **5e** in toluene or *p*-xylene solvent at 130 ^oC. These reactions yielded the bis γ-C(sp^2)-H arylated phenylglycinol derivative **8a**-(*R*) in 50-65% yields and the mono γ-C(sp^2)-H arylated phenylglycinol derivative **8aa**-(*R*) in 10% yield (entries 19 and 20, Table 1). Finally, we performed the Pd(II)-catalyzed AgOAc-promoted C-H arylation of enantiopure substrate **4a**-(*R*) by using 4 equiv of **5e** in toluene (at 110 ^oC) or *p*-xylene (at 130 ^oC). These reactions selectively yielded the enantiopure bis γ-C(sp^2)-H arylated phenylglycinol derivative **8a**-(*R*) in 70-96% yields with only traces of the mono γ-C(sp^2)-H arylated phenylglycinol derivative **8aa**-(*R*) (entries 21 and 22, Table 1).

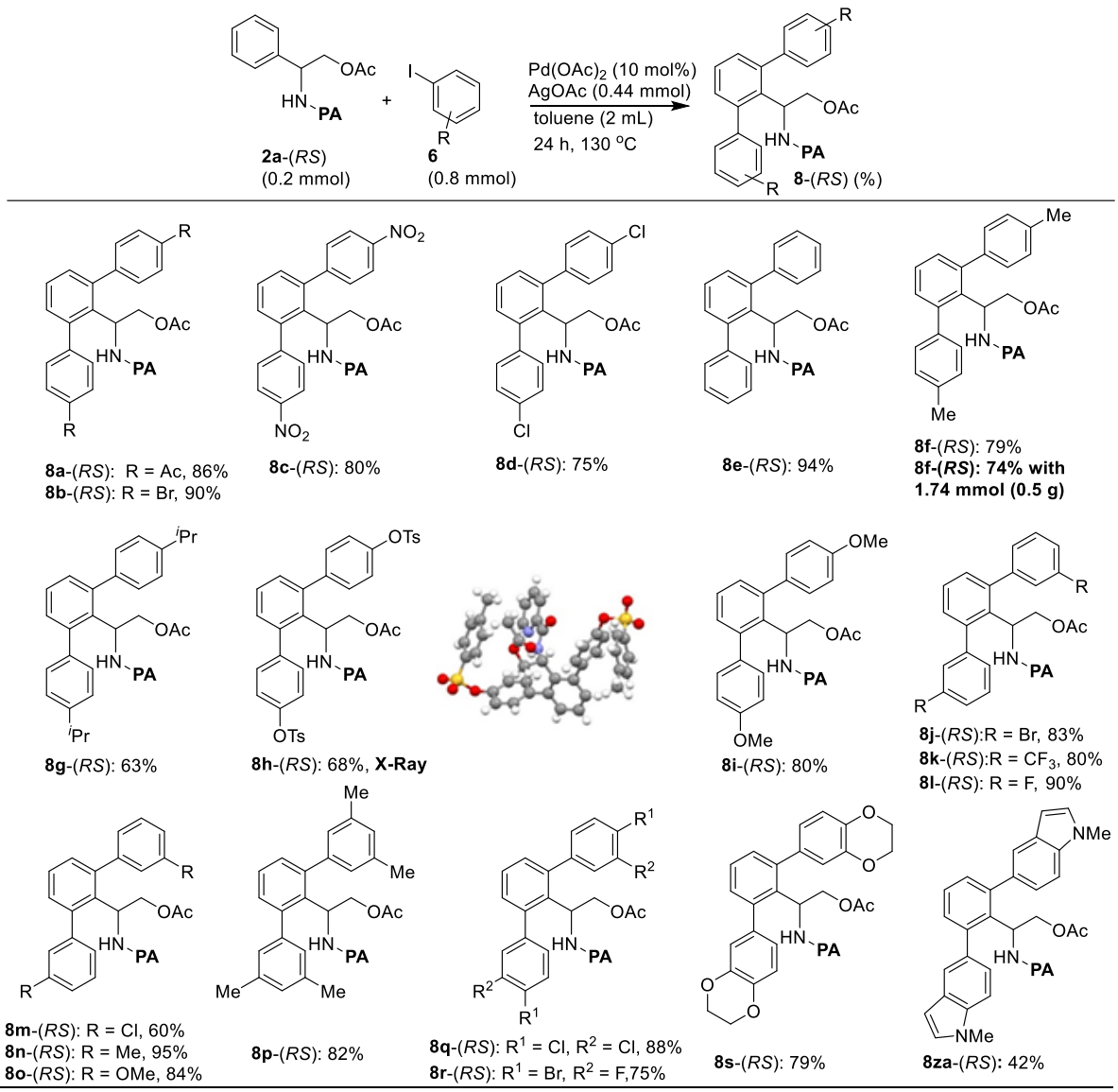
Table 1: Optimization reaction of reaction condition. Pd-(II) catalyzed γ-C(sp^2)-H arylation of enantiopure phenylglycinol substrate **4a**-(*R*)



entry	PdL_2	**5e** (mmol)	additive	*T* (°C)	**8aa**-(*R*)**:** Yield (%)	**8a**-(*R*)**:** Yield (%)
1	$Pd(OAc)_2$	0.3	AgOAc	110	7	60
2[a]	$Pd(OAc)_2$	0.3	AgOAc	110	0	16
3[b]	$Pd(OAc)_2$	0.3	AgOAc	110	8	42
4[c]	$Pd(OAc)_2$	0.3	AgOAc	110	10	56
5	$PdCl_2$	0.3	AgOAc	110	traces	26
6	$Pd(TFA)_2$	0.3	AgOAc	110	23	25
7	$Pd(AcAc)_2$	0.3	AgOAc	110	0	0
8	$PdCl_2(Ph_3P)_2$	0.3	AgOAc	110	0	0
9	$PdCl_2(MeCN)_2$	0.3	AgOAc	110	7	31
10	$PdCl_2(PhCN)_2$	0.3	AgOAc	110	traces	30
11	$Pd(dba)_2$	0.3	AgOAc	110	traces	22
12	$Pd(OAc)_2$	0.3	Ag_2CO_3	110	<5	30
13	$Pd(OAc)_2$	0.3	Ag_2O	110	0	8
14	$Pd(OAc)_2$	0.3	$PhI(OAc)_2$	110	0	0
15	$Pd(OAc)_2$	0.3	K_2CO_3	110	18	13
16[d]	$Pd(OAc)_2$	0.3	KOAc	110	41	20
17[e]	$Pd(OAc)_2$	0.3	AgOAc	100	8	25
18[f]	$Pd(OAc)_2$	0.3	AgOAc	100	7	28
19	$Pd(OAc)_2$	0.3	AgOAc	130	10	50
20[g]	$Pd(OAc)_2$	0.3	AgOAc	130	10	65
21	$Pd(OAc)_2$	0.8	AgOAc	110	traces	70
22[h]	**$Pd(OAc)_2$**	**0.8**	**AgOAc**	**130**	**traces**	**96**

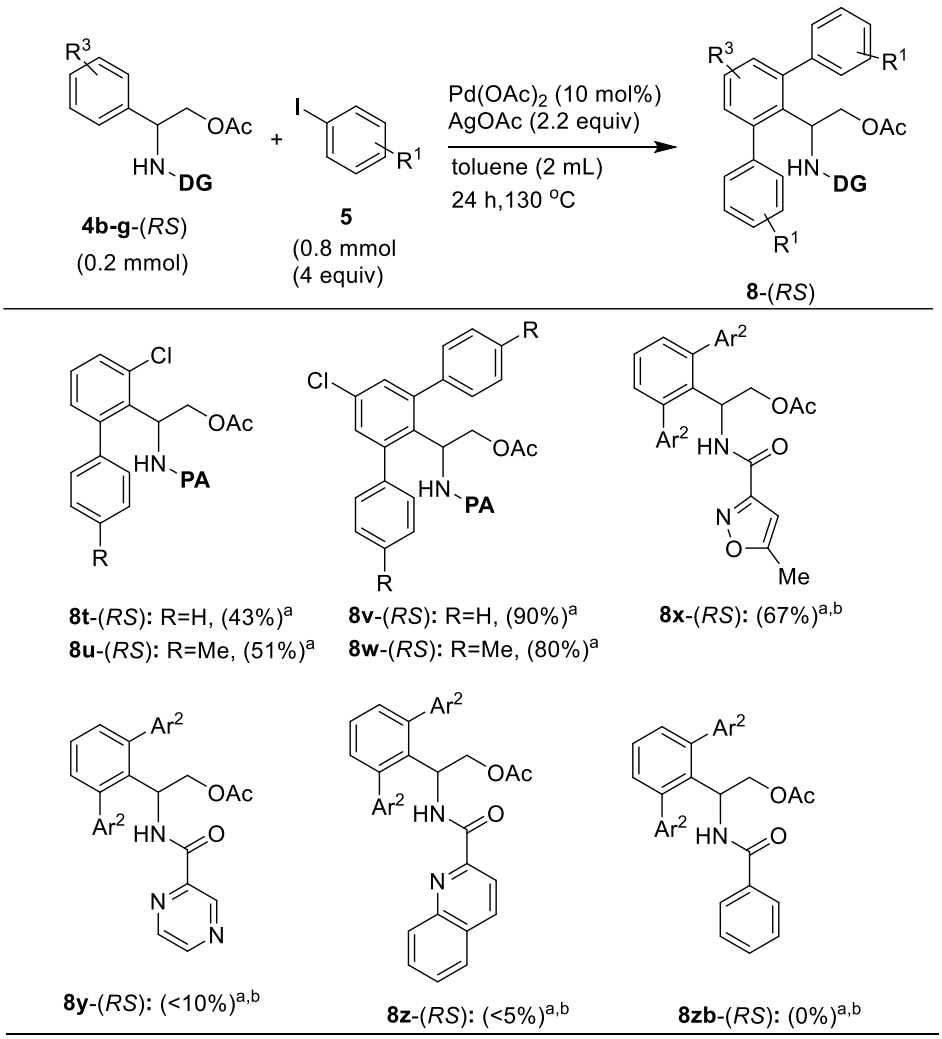
[a] $Pd(OAc)_2$ (5 mol%). [b] PivOH (0.04 mmol). [c] $(BnO)_2PO_2H$ (0.04 mmol). [d] **8aa**-(*R*) (*ee* 96%) was obtained from **4a**-(*R*) (*ee* 98%). Furthermore, we also prepared the corresponding mono-arylated product **8aa**-(*S*) (37%, *ee* 95%) from **4a**-(*S*) (*ee* 98%) using the conditions of entry 16. Additionally, we prepared the corresponding racemic mono-arylated product **8aa**-(*RS*) (35%) from **4a**-(*RS*) using the conditions of entry 16. [e]*t*-AmylOH. [f]1,4-Dioxane. [g]*p*-Xylene. [h]**8a**-(*R*) (*ee* >97%) was obtained from **4a**-(*R*) (*ee* 98%).

Having done the optimization reactions, next we planned to explore the substrate scope and generality of this protocol comprising of the Pd(II)-catalyzed, picolinamide-aided *ortho*-C-H/ γ-C(sp^2)-H functionalization of phenylglycinol substrates. In this regard we preformed the $Pd(OAc)_2$-catalyzed AgOAc-promoted γ-C(sp^2)-H arylation of racemic phenylglycinol substrate **4a**-(*RS*) with aryl iodides possessing different substituents at the *m/p* positions. These reactions gave the corresponding bis *ortho*-C-H arylated phenylglycinol derivatives **8a-o**-(*RS*) in 60-95% yields. Next, the arylation of substrate **4a**-(*RS*) with different disubstituted aryl iodides and 5-iodoindole afforded the corresponding bis *ortho*-C-H arylated phenylglycinol derivatives **8p-s**-(*RS*) and **8za**-(*RS*) in 42-88% yields. The Pd(II)-catalyzed, picolinamide-aided γ-C(sp^2)-H arylation of phenylglycinol derivative **4a**-(*RS*) with *p*-tolyl iodide was performed in a slightly large scale (0.5 g scale), which yielded the bis γ-C(sp^2)-H arylated phenylglycinol derivative **8f**-(*RS*) in 74% yield (Scheme 4).



Scheme 4: Substrate scope investigation. Synthesis of various racemic bis *γ*-C-H arylated of phenylgylcinol scaffolds 8a-8za-(*RS*)

Having done the Pd(II)-catalyzed arylation reactions by using the picolinamide directing group, next we wished to test the *γ*-C(sp^2)-H arylation of phenylglycinol substrates by using different directing groups. We performed the Pd(II)-catalyzed arylation of phenylglycinol substrates **4d**-(*RS*) containing the 5-methylisoxazole-3-carboxamide (MICA) directing group. Accordingly, the Pd(II)-catalyzed MICA DG-aided arylation of **4d**-(*RS*) afforded the corresponding *ortho*-C-H arylated phenylglycinol derivatives **8x**-(*RS*) in 67% yields (Scheme 5).

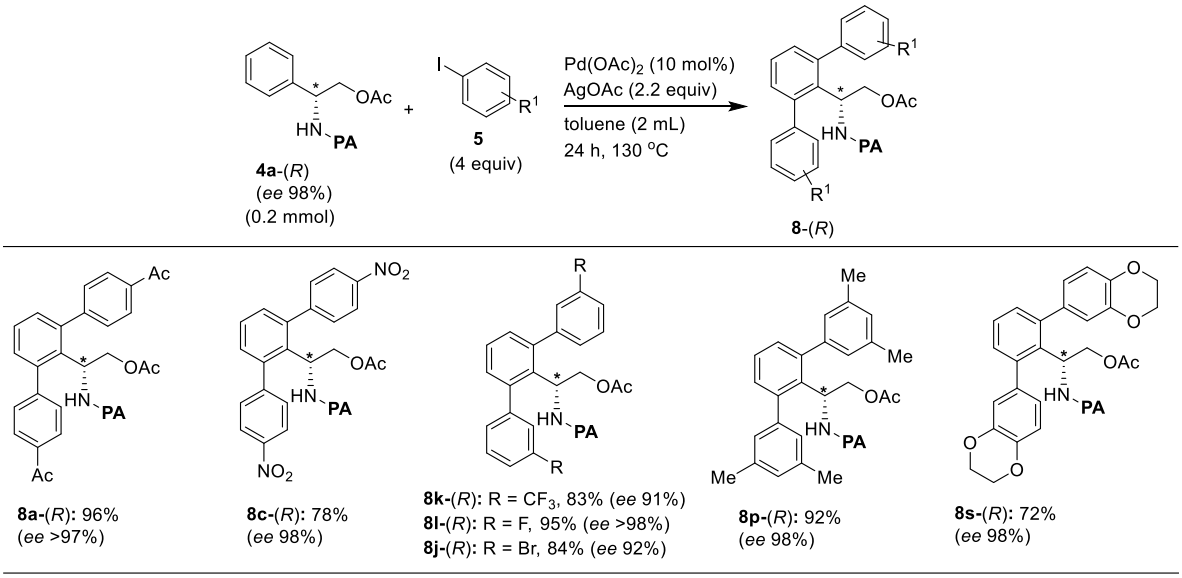


[a] Conditions for reactions involving substrates **4b-g**-(*RS*): Substrate (0.2 mmol), ArI (0.8 mmol), $Pd(OAc)_2$ (10 mol%), AgOAc (0.44 mmol), toluene (2 mL), 24 h, 130 °C. [b] Ar^2 = 4-(Ac)-C_6H_4.

Scheme 5: Directing group and substrate scope investigation. The *γ*-C-H arylation of various **4b-g**-(*RS*) phenylglycinols.

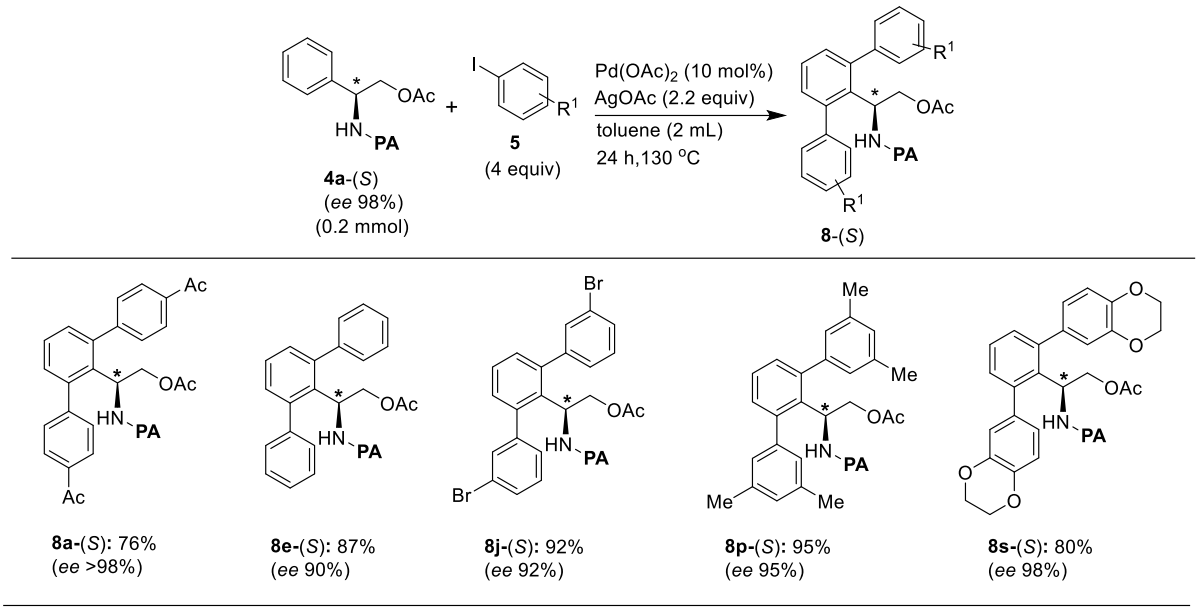
Next, the Pd(II)-catalyzed arylation of phenylglycinol substrates **4f**-(*RS*) containing the pyrazine-2-carboxamide directing group were performed. These reactions afforded the corresponding bis *ortho*-C-H arylated phenylglycinol derivative **8y**-(*RS*) in low yields (<10%). The Pd(II)-catalyzed arylation of phenylglycinol substrates **4e**-(*RS*) containing the quinoline-2-carboxamide directing group did not yield the corresponding products **8z**-(*RS*). Similarly, the Pd(II)-catalyzed arylation of phenylglycinol substrates **4g**-(*RS*) containing the simple amide directing groups did not yield the corresponding products **8zb**-(*RS*). Overall, the reactions that have been shown in Scheme 4 and the screening of various directing groups (Scheme 5) indicated that the picolinamide is the better directing group for the *γ*-C(sp^2)-H arylation of

phenylglycinol substrates. The Pd(II)-catalyzed, picolinamide-aided arylation of *o-/p*-chlorophenylglycinol substrates **4b**-(*RS*) and **4c**-(*RS*) with different aryl iodides found to afford the corresponding *ortho*-C-H arylated phenylglycinol derivatives **8t-w**-(*RS*) in 43-90% yields. bis C-H arylated phenylglycinol derivatives **8a,c,j,k,l,p,s**-(*R*) in 72-96% yields with good enantiopurities (*ee* 91-98%, Scheme 6). The Pd(II)-catalyzed picolinamide-aided arylation of enantiopure phenylglycinol substrate **4a**-(*R*) was carried out using various aryl iodides containing different substituents at the *meta*/*para* positions and disubstituted aryl iodides. These reactions yielded the corresponding enantiopure bis C-H arylated phenylglycinol derivatives **8a,c,j,k,l,p,s**-(*R*) in 72-96% yields with good enantiopurities (*ee* 91-98%, Scheme 6).



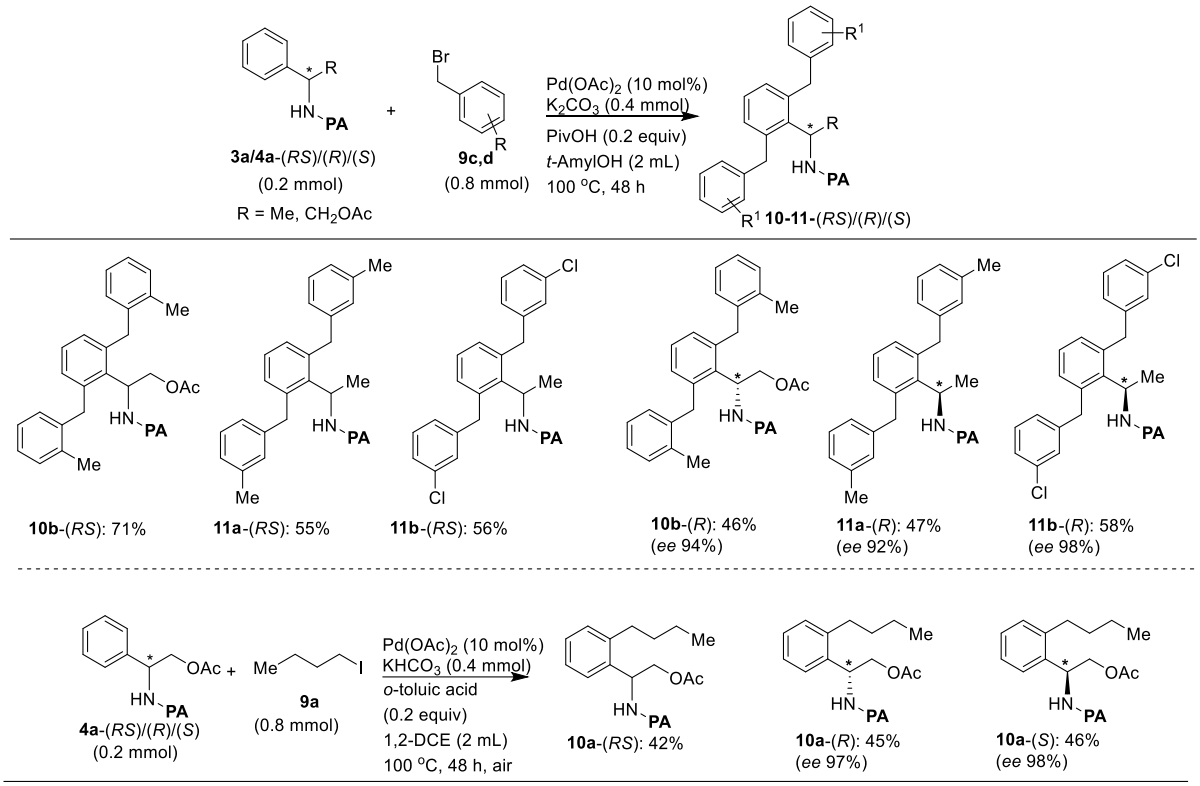
Scheme 6: Substrate scope investigation: Synthesis of γ-C-H arylated (*R*)-phenylglycinols scaffolds.

Next, we performed the Pd(II)-catalyzed, picolinamide-aided arylation reactions using the substrates prepared from (*S*)-phenylglycinol substrates. The corresponding bis C-H arylated phenylglycinol derivatives **8a,e,j,p,s**-(*S*) were obtained in 76-95% yields with good enantiopurities (*ee* 90->98%) from the arylation of enantiopure phenylglycinol substrate **4a**-(*S*) (Scheme 7).



Scheme 7: Substrate scope investigation: Synthesis of *γ*-C-H arylated (*S*)-phenylglycinols scaffolds.

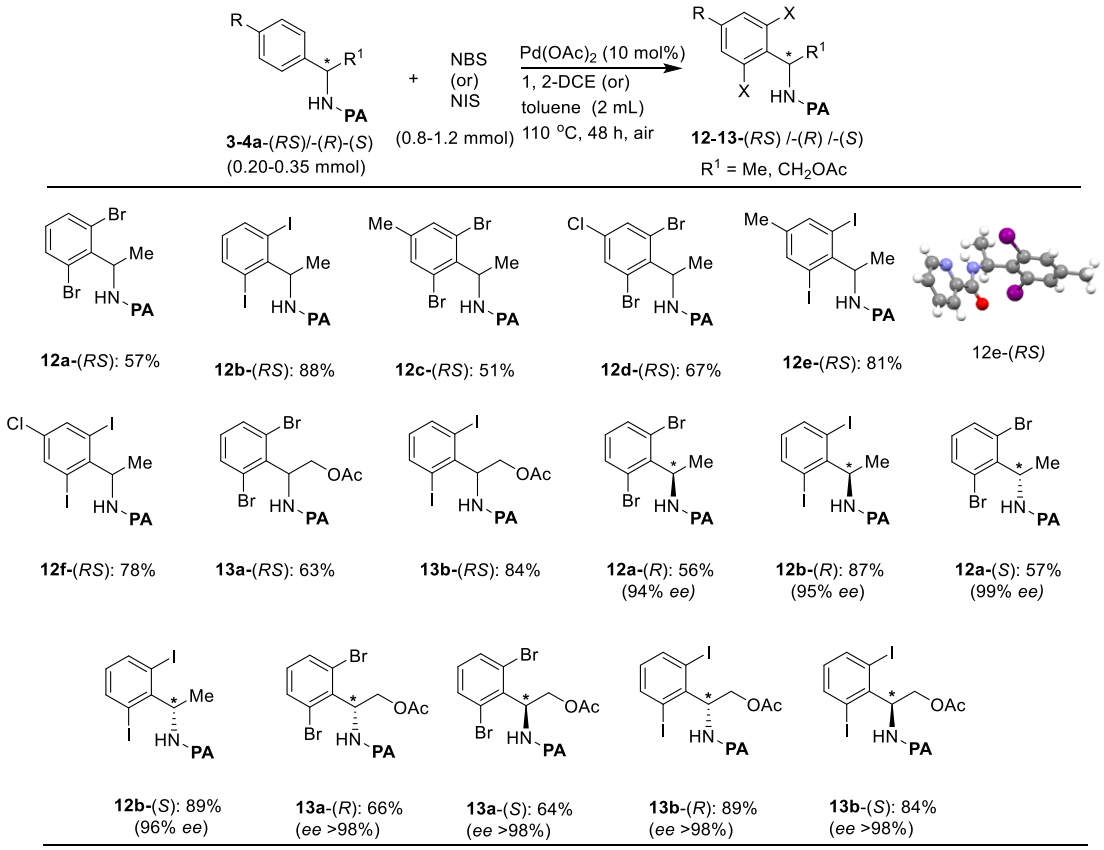
We extended the scope of this protocol concerning the *γ*-C(sp^2)-H functionalization of enantiopure *α*-methylbenzylamine and phenylglycinol substrates by attempting the alkylation/benzylation, bromination and iodination reactions. An initial attempt involving the Pd(II)-catalyzed alkylation of phenylglycinol substrate **4a**-(*RS*) with alkyl iodide **9a** afforded the mono *γ*-C(sp^2)-H alkylated product **10a**-(*RS*) in 42% yield (Scheme 8). This observation is in concurrence with the previous report by Jiang. Jiang reported[6d] a few examples of picolinamide-aided *ortho*-C-H alkylation of phenylglycine substrate, which selectively yielded the mono C-H alkylated phenylglycines in 42-50% yields. On the other hand, the Pd(II)-catalyzed benzylation of phenylglycinol substrate **4a**-(*RS*) with benzyl bromide **9b** afforded the bis *γ*-C(sp^2)-H benzylated product **10b**-(*RS*) in 71% yield. Subsequently, we performed the Pd(II)-catalyzed alkylation of enantiopure phenylglycinol substrates **4a**-(*R*) and **4a**-(*S*) with alkyl iodide **9a**. These attempts afforded the corresponding mono *γ*-C(sp^2)-H alkylated phenylglycinols **10a**-(*R*) and **10a**-(*S*) in 45-46% yields with good enantiopurities (*ee* 97-98%, Scheme 8). The Pd(II)-catalyzed benzylation of enantiopure phenylglycinol substrate **4a**-(*R*) with benzyl bromide **9b** yielded bis *γ*-C(sp^2)-H benzylated phenylglycinols **10b**-(*R*) in 46% yield with good enantiopurity (*ee* 94%, Scheme 8).



Scheme 8: Pd-(II) catalyzed γ-C-H alkylation/benzylation of racemic and enantiopure α-methylbenzylamines and phenylglycinols

Similarly, The Pd(II)-catalyzed benzylation of enantiopure α-methylbenzylamine substrate **3a**-(*R*) with benzyl bromides **9c,d** yielded the corresponding enantiopure bis γ-C(sp^2)-H benzylated α-methylbenzylamines **11a**-(*R*) and **11b**-(*R*) in 47-58% yields with good enantiopurities (*ee* 92-98%, Scheme 8). To establish the HPLC pattern of **11a**-(*R*) and **11b**-(*R*), the corresponding racemic bis γ-C(sp^2)-H benzylated α-methylbenzylamines **11a**-(*RS*) and **11b**-(*RS*) were also obtained in 55-56% yields via the $Pd(OAc)_2$-catalyzed, AgOAc-promoted γ-C(sp^2)-H benzylation of **3a**-(*RS*). Earlier, Daugulis reported[9e] the picolinamide-aided alkylation and benzylation of racemic α-methylbenzylamine by using the combination of $Pd(OAc)_2$ (10 mol%) and $CuBr_2$ (20 mol%) in the presence of K_2CO_3. We then attempted the Pd(II)-catalyzed, picolinamide-aided *ortho* C-H bromination and iodination of racemic and enantiopure α-methylbenzylamine and phenylglycinol substrates (Scheme 9). The Pd(II)-catalyzed bromination and iodination of racemic α-methylbenzylamine substrates **3a**-(*RS*), **3b**-(*RS*) and **3c**-(*RS*) with NBS or NIS yielded the corresponding racemic bis γ-C(sp^2)-H brominated and iodinated α-methylbenzylamine derivatives **12a,c,d**-(*RS*) and **12b,e,f**-(*RS*) in 51-88% yields (Scheme 9). The X-ray structure analysis unambiguously confirmed the structure of a representative γ-C(sp^2)-H iodinated α-methylbenzylamine derivative **12e**-

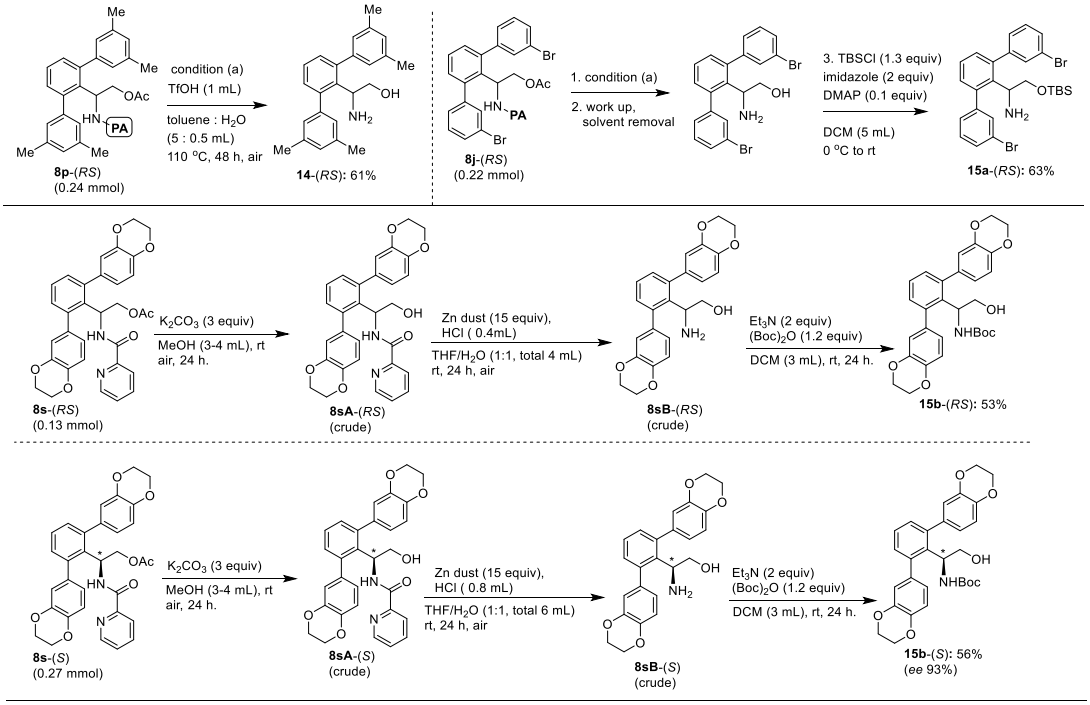
(RS).[16] Subsequently, the Pd(II)-catalyzed *ortho* C-H bromination and iodination of enantiopure *α*-methylbenzylamine substrates **3a**-(*R*) and **3a**-(*S*) with NBS or NIS yielded the corresponding bis *γ*-C(sp^2)-H brominated and iodinated *α*-methylbenzylamine derivatives **12a**-(*R*), **12b**-(*R*), **12a**-(*S*) and **12b**-(*S*) in 56-89% yields with good enantiopurities (*ee* 94-99%, Scheme 9). Similarly, the Pd(II)-catalyzed, picolinamide-aided *ortho* C-H bromination and iodination of racemic phenylglycinol substrate **4a**-(*RS*) with NBS or NIS yielded the corresponding racemic bis *γ*-C(sp^2)-H brominated and iodinated phenylglycinol derivatives **13a,b**-(*RS*) in 63-84% yields (Scheme 9). The Pd(II)-catalyzed *ortho* C-H bromination and iodination of enantiopure phenylglycinol substrates **4a**-(*R*) and **4a**-(*S*) with NBS or NIS also yielded the corresponding bis *γ*-C(sp^2)-H brominated and iodinated phenylglycinol derivatives **13a**-(*R*), **13b**-(*R*), **13a**-(*S*) and **13b**-(*S*) in 64-89% yields with good enantiopurity (*ee* >98%, Scheme 9).



Scheme 9: Pd-(II) catalyzed *γ*-C-H bromination and iodination of racemic and enantiopure *α*-methylbenzylamines and phenylglycinols. X-ray structure (ball and stick model) of compound 12e.

We also attempted the removal of the picolinamide directing group after performing the Pd(II)-catalyzed *γ*-C(sp^2)-H arylation of *α*-methylbenzylamine and phenylglycinol substrates. Various

attempts were made to find out the better reaction conditions for removing the picolinamide directing group. Out of all trials, the treatment of the γ-C(sp^2)-H arylated phenylglycinol derivative **8p**-(*RS*) with TfOH in toluene/H_2O mixture at 110 ^oC for 48 h, yielded the picolinamide DG-free racemic phenylglycinol **14**-(*RS*) in 61% yield (Scheme 10). Another trial involving a sequential process comprising the removal of picolinamide moiety from the γ-C(sp^2)-H arylated phenylglycinol derivative **8j**-(*RS*) followed by protection of the OH group yielded the picolinamide DG-free TBS-protected phenylglycinol (OTBS derivative) **15a**-(*RS*) in 63% yield. Subsequently, we prepared the corresponding enantiopure phenylglycinol **14**-(*R*) and TBS-protected phenylglycinol **15a**-(*R*). However, due to poor peak separation in different chiral columns, we could not establish the HPLC patterns of both the racemic/enantiopure phenylglycinol derivatives **14**-(*RS*) or **14**-(*R*) and TBS-protected phenylglycinol derivatives **15a**-(*RS*) or **15a**-(*R*). Thus, we tried another method to remove the picolinamide to establish the HPLC patterns of by using the racemic/enantiopure phenylglycinol derivatives **8s**-(*RS*) and **8s**-(S). Deprotection of acetyl group of **8s**-(*RS*) with K_2CO_3 gave the crude compound **8sA**-(*RS*). Then, Zn dust-mediated removal of picolinamide group from **8sA**-(*RS*) gave the crude phenylglycinol derivative **8sB**-(*RS*). Then, the Boc protection of the NH_2 group gave the *N*-Boc compound **15b**-(*RS*). We could obtain the HPLC pattern for the compound **15b**-(*RS*). Accordingly, we prepared the enantiopure *N*-Boc-protected phenylglycinol derivative **15b**-(*S*) (Scheme 10).



Scheme 10: Removal of picolinamide DG from γ-C-H arylated picolinamide derivatives.

In summary, we have reported our efforts toward expanding the library of both racemic and enantiopure *α*-methylbenzylamine and phenylglycinol scaffolds *via* the Pd(II)-catalyzed, picolinamide DG-aided sp^2 *γ*-C-H functionalization. Primarily, we were interested in expanding the library of enantiopure *α*-methylbenzylamine and phenylglycinol scaffolds via the sp^2 *γ*-C-H arylation-, alkylation-, halogenation (bromination and iodination) of *α*-methylbenzylamine and phenylglycinol substrates. We have shown the synthesis of a wide range of racemic and enantiopure sp^2 *γ*-C-H arylated, alkylated, brominated, and iodinated *α*-methylbenzylamine and phenylglycinol scaffolds. In general, we obtained both the *R* and *S* chiral sp^2 *γ*-C-H functionalized *α*-methylbenzylamine and phenylglycinol scaffolds with good enantiopurities. To the best of our knowledge, there is no literature report dealing with the Pd(II)-catalyzed picolinamide-aided DG-aided arylation and halogenation of sp^2 *γ*-C-H bonds of enantiopure *α*-methylbenzylamine and phenylglycinol substrates. Considering the importance of racemic and enantiopure *α*-methylbenzylamine and phenylglycinol derivatives in organic synthesis and medicinal chemistry, this work on assembling racemic and enantiopure *ortho*-C-H functionalized *α*-methylbenzylamine and phenylglycinol scaffolds via the C-H functionalization route might be a valuable contribution.

General. Reactions were done in oven-dried round-bottom flasks/sealed tubes in anhydrous solvents under a nitrogen atmosphere. TLC analyses were performed on silica gel or silica gel 60 F_{254} pre-coated plates and components were visualized with exposure to iodine vapour or by irradiation under a UV lamp. The column chromatography purification was performed using silica gel (100-200 mesh) or neutral alumina (eluent = ethyl acetate:hexane). ^1H NMR and $^{13}C\{^1H\}$ spectra of samples have been recorded on 400 and ~101 MHz (or 500 and ~126 MHz) spectrometers, respectively (using TMS as an internal standard)and $^{19}F\{^1H\}$ NMR was recorded on ~376 MHz spectrometer. In some of the ^1H and $^{13}C\{^1H\}$ NMR spectra of a few samples, we observed the broadening of a few signals. The HRMS data were obtained from QTOF mass analyser using the electrospray ionization (ESI) method. The IR spectra of samples have been recorded either as neat samples or using KBr pellets or in an appropriate solvent. For finding the specific rotations of enantiopure samples, the solutions were prepared in DCM or $CHCl_3$. Polarimeter analysis data were recorded at 589 nm wavelength using 100 mm cell length, concentration (*c*) taken as g/100 mL. HPLC analysis was carried out on isolated samples. In Table 1, in almost all the entries the product **8a**-(*R*) was isolated. However, the HPLC analysis was carried out for **8a**-(*R*) obtained in entry 22 only (though we used **4a**-(*R*) (*ee* 98%) for all entries). Similarly, the product **8aa**-(*R*) (*ee* 96%) was obtained from **4a**-(*R*) (*ee*

98%) in entry 16. We also prepared the corresponding mono-arylated product **8aa**-(*S*) (37%, *ee* 95%) from **4a**-(*S*) (*ee* 98%) using the conditions of entry 16. Additionally, we prepared the corresponding racemic mono-arylated product **8aa**-(*RS*) (35%) from **4a**-(*RS*) using the conditions of entry 16. All the yields reported are isolated yields and the yields are not optimized. Sometimes there are marginal variations in yields for the racemic/enantiopure pairs. This is perhaps due to inadvertent handling/processing errors and manual gathering of all possible pure fractions (during column chromatographic purification). While there seems to be partial racemization under the experimental conditions, the observed best *ee* values in HPLC analysis are reported. The observed *ee* was checked for some typical pairs by repeating the reaction another time. For example, the arylation reactions affording the corresponding pairs **8p**-(*R*), **8p**-(*S*) and **8a**-(*R*), **8a**-(*S*) were run two times. In a typical case, for the pairs, **8p**-(*R*), **8p**-(*S*) independent HPLC analysis showed comparable results with marginal changes.

Procedure for the preparation of the OAc-protected picolinamide-installed phenylglycinol carboxamides 4 (Procedures A and B): ***Procedure A****:* An appropriate amount of aromatic or heteroaromatic carboxylic acid (5 mmol, ligand), *N,N'*-dicyclohexylcarbodiimide (1.1 equiv), 1-hydroxybenzotriazole hydrate (1.1 equiv) in DCM (20 mL) were stirred at 0 ^{o}C for 1 h under a nitrogen atmosphere. Then an appropriate amount of phenylglycinol (1 equiv) was added to the above mixture and stirred at rt for 24 h. Then, the resulting solution was subjected to an aq. workup and washed with aq. sodium bicarbonate solution (two times). Then, the resultant crude reaction mixture was purified on silica gel column chromatography to obtain corresponding (OH group free) phenylglycinol carboxamide, which was then used in the next step.

Procedure B*:* Then, an appropriate amount of (OH group free) phenylglycinol carboxamide prepared in the above step, was dissolved in dry DMF followed by the addition of 4-(dimethylamino)pyridine (0.1 equiv) and acetic anhydride (1.1 equiv), and the resulting reaction mixture was stirred overnight at rt under a nitrogen atmosphere. Then, the resulting solution was diluted with water and was extracted with ethyl acetate, and the combined organic phase was washed with brine solution. The resulting solution was then concentrated and purified on silica gel column chromatography (eluent = EtOAc:hexane) to give the corresponding alcohol group acetylated phenylglycinol carboxamide.

General procedure for the preparation of *α*-methyl benzylamine carboxamides (3a-c): An appropriate amount of carboxylic acid (1-5 mmol), *N,N'*-dicyclohexylcarbodiimide (1.1 equiv), 1-hydroxybenzotriazole hydrate (1.1 equiv) in DCM (10-20 mL) were stirred at 0 ^{o}C

for 1 h under a nitrogen atmosphere. An appropriate amount of *α*-methyl benzylamine (1 equiv) was added and stirred at rt for 24 h. Then, the resulting solution was subjected to an aq. workup and washed with aq. sodium bicarbonate solution (two times). The resulting crude reaction mixture was purified by using silica gel column chromatography to obtain corresponding carboxamides.

General procedure for the Pd(II)-catalyzed *ortho* C-H arylation of picolinamide derived from phenylglycinol (Procedure C): A mixture of an appropriate carboxamide derived from phenylglycinol or *α*-methyl benzylamine (1 equiv), an appropriate aryl iodide (4 equiv), $Pd(OAc)_2$ (10 mol%) and AgOAc (2.2 equiv) in anhydrous toluene (2-3 mL) was heated at 130 ^oC for 24 h under a nitrogen atmosphere. After the reaction period, the reaction mixture was concentrated in a vacuum. Purification of the resulting reaction mixture by column chromatography on silica gel (eluent = EtOAc:hexane) gave the corresponding *ortho* C-H arylated phenylglycinol derivative.

Procedure for the Pd(II)-catalyzed *ortho* C-H benzylation of carboxamide derived from phenylglycinol or *α*-methyl benzylamine (Procedure D): A mixture of an appropriate carboxamide derived from phenylglycinol or *α*-methyl benzylamine (1 equiv), an appropriate benzyl bromide (4 equiv), $Pd(OAc)_2$ (10 mol%), K_2CO_3 (2 equiv) and PivOH (0.2-0.4 equiv) in anhydrous *t*-amylOH (2 mL) was heated at 100 ^oC for 36-48 h under a nitrogen atmosphere. Then, the workup and purification were carried out as mentioned in procedure C.

General procedure for the Pd(II)-catalyzed *ortho* C-H bromination of carboxamide derived from phenylglycinol or *α*-methyl benzylamine (Procedure E): A mixture of an appropriate carboxamide derived from phenylglycinol or *α*-methyl benzylamine (1 equiv), *N*-bromosuccinimide (4 equiv), $Pd(OAc)_2$ (10 mol%) in anhydrous 1,2-DCE (2 mL) was heated at 110 ^oC for 48 h in air. Then, the workup and purification were carried out as mentioned in procedure C.

General procedure for the Pd(II)-catalyzed *ortho* C-H iodination of carboxamide derived from phenylglycinol or *α*-methyl benzylamine (Procedure F): A mixture of an appropriate carboxamide derived from phenylglycinol or *α*-methyl benzylamine (1 equiv), *N*-iodosuccinimide (4 equiv), $Pd(OAc)_2$ (10 mol%) in anhydrous toluene (2 mL) was heated at 110 ^oC for 48 h in air. Then, the workup and purification were carried out as mentioned in procedure C.

General procedure for the Pd(II)-catalyzed *ortho* C-H alkylation of phenylglycinol carboxamide (Procedure G): A mixture of an appropriate phenylglycinol carboxamide (1

equiv), 1-iodobutane (4 equiv), $Pd(OAc)_2$ (10 mol%), $KHCO_3$ (2 equiv) and *o*-toluic acid (0.2 equiv) in anhydrous 1,2-DCE (2 mL) was heated at 100 ^oC for 48 h in air. Then, the workup and purification were carried out as mentioned in procedure C.

The typical procedure for the removal of picolinamide directing group after C-H arylation of phenylglycinol derivative (Procedure H): An appropriate amount of *ortho* C-H arylated phenylglycinol carboxamide (1 equiv) was taken in a reaction flask/tube, in which trifluoromethanesulfonic acid (1 mL), and toluene:H_2O (5 mL: 0.5 mL) were added under air. The reaction mixture was stirred at 110 ^oC for 48 h. After the reaction period, the reaction mixture was cooled to rt and quenched by slowly adding a saturated solution of Na_2CO_3 (10 mL). The aqueous phase was extracted with EtOAc (3 times), evaporation of the solvent, and purification of the resulting reaction mixture by column chromatography on silica gel (eluent = EtOAc:hexane) gave the corresponding directing group-free C-H arylated phenylglycinol (e.g., **14**-(*RS*).

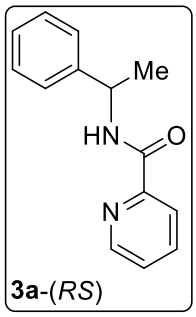
The typical procedure for the sequential removal of picolinamide directing group after C-H arylation of phenylglycinol derivative and TBS protection of the OH group (Procedure I): The resulting crude mixture obtained in procedure H was directly dissolved in dry DCM (5 mL) and cooled to 0 ^oC. Then, imidazole (2 equiv), DMAP (0.1 equiv) and TBSCl (1.3 equiv) were added, and the resulting solution was stirred at rt for 24 h under a nitrogen atmosphere. After this period, the reaction mixture was quenched with saturated $NaHCO_3$ solution. The organic layers were washed with $NaHCO_3$ solution and brine solution. Evaporation of solvent and purification of the resulting crude material on silica gel column to (eluent = EtOAc:hexane) afforded the corresponding *O*-TBS protected, free amine-based phenylglycinol derivative (e.g., **15a**-(*RS*).

The typical procedure for the deacetylation of the OAc group after C-H arylation of phenylglycinol derivative (Procedure J): An appropriate amount of *ortho* C-H arylated phenylglycinol carboxamide (1 equiv) was dissolved in MeOH (2-4 mL). To this solution, K_2CO_3 (3 equiv) was added, and the reaction mixture was stirred at rt for 24 h in air. Then, the reaction mixture was diluted with water and extracted with EtOAc (three times), and the organic layers were dried over anhydrous Na_2SO_4. The resulting solution was then concentrated and used for the next step without further purification.

The typical procedure for the removal of picolinamide directing group from C-H arylated phenylglycinol and Boc protection of the NH_2 group (Procedure K): To an appropriate picolinamide of phenylglycinol (1 equiv) dissolved in H_2O/THF (1:1, 4-6 mL) 12 M HCl (0.4-

0.95 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 24 h. The reaction was filtered through a celite plug. The filtrate was transferred to a separating funnel with 2 M NaOH (50 mL) and extracted with DCM. The reaction mixture was concentrated in a vacuum and used for the next step. An appropriate amount of picolinamide directing group removed phenylglycinol carboxamide obtained in the above procedure (1 equiv), Et_3N (2 equiv), Boc_2O (1.2-2.0 equiv) were dissolved DCM (5 mL), and the reaction mixture was stirred at rt for 24 h under a nitrogen atmosphere. Work-up using the brine solution, evaporation of solvent gave a crude mixture, which was purified on silica gel column chromatography to afford corresponding *N*-Boc phenylglycinol derivative.

_N_-(1-Phenylethyl)picolinamide (3a-(_RS_)):[9e]



3a-(*RS*)

The compound **3a**-(*RS*) was obtained as a colourless solid (650 mg, 96%, 3.0 mmol scale). R_f = 0.5 (EtOAc/hexane= 20:80); mp: 134-136 ^oC.

IR (DCM): 3379, 1670, 1510 cm^{-1}.

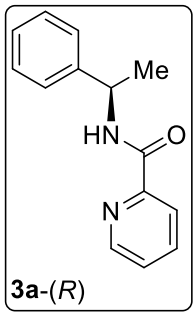
^1H NMR (400 MHz, $CDCl_3$): δ = 8.54-8.52 (m, 1H), 8.34 (d, 1H, J = 6.8 Hz), 8.19 (dt, 1H, J_1 = 7.8, J_2 = 0.9 Hz), 7.82 (td, 1H, J_1 = 7.7, J_2 = 1.7 Hz), 7.42-7.38 (m, 3H), 7.36-7.33 (m, 2H), 7.28-7.24 (m, 1H), 5.36-5.29 (m, 1H), 1.62 (d, 3H, J = 7.0 Hz).

$^{13}C\{^1H\}$ NMR (~101 MHz, $CDCl_3$): δ = 163.4, 149.9, 148.0, 143.3, 137.4, 128.7, 127.3, 126.2, 126.2, 122.3, 48.8, 22.1.

HRMS (ESI): *m/z* $[M+Na]^+$ calcd for $C_{14}H_{14}N_2NaO$: 249.1004; found: 249.1015.

The HPLC of compound **3a**-(*RS*) was determined by using the Daicel Chiralpak IC column, hexane/*i*-PrOH 90:10, flow rate 1.0 mL/min, UV detection at 254 nm, t_R = 19.27 min, t_S = 29.83 min.

(_R_)-_N_-(1-Phenylethyl)picolinamide (3a-(_R_)):[11b]



3a-(*R*)

The compound **3a**-(*R*) was obtained as a colourless solid (600 mg, 88%, 3.0 mmol scale).

R_f = 0.5 (EtOAc/hexane= 20:80); mp: 134-136 ^oC.

IR (DCM): 3382, 1670, 1510 cm^{-1}.

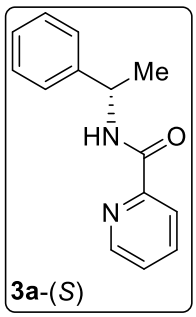
^1H NMR (400 MHz, $CDCl_3$): δ = 8.54-8.52 (m, 1H), 8.34 (d, 1H, J = 6.9 Hz), 8.19 (dt, 1H, J_1 = 7.8, J_2 = 1.0 Hz), 7.82 (td, 1H, J_1 = 7.7, J_2 = 1.7 Hz), 7.42-7.38 (m, 3H), 7.36-7.33 (m, 2H), 7.28-7.24 (m, 1H), 5.36-5.29 (m, 1H), 1.62 (d, 3H, J = 7.0 Hz).

$^{13}C\{^1H\}$ NMR (~101 MHz, $CDCl_3$): δ = 163.3, 149.8, 147.9, 143.2, 137.3, 128.6, 127.2, 126.1, 126.1, 122.2, 48.7, 22.0.

$[\alpha]^{25}_D$ = -7.23 (c = 0.10, DCM).

The enantiomeric excess (*ee* 97%) of compound **3a**-(*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 = 17.94 min, t_S = 28.66 min.

(*S*)-*N*-(1-Phenylethyl)picolinamide (**3a-(*S*)**):[11f]



The compound **3a**-(*S*) was obtained as a colourless solid (540 mg, 80%, 3.0 mmol scale).

R_f = 0.5 (EtOAc/hexane= 20:80). mp: 134-136 ^oC.

IR (DCM): 3381, 1670, 1510 cm^{-1}.

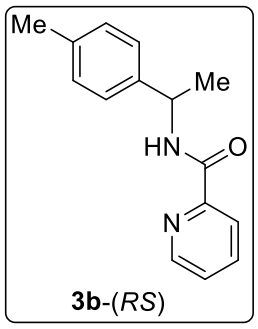
^1H NMR (400 MHz, $CDCl_3$): δ = 8.52-8.51 (m, 1H), 8.33 (d, 1H, J = 6.9 Hz), 8.19 (d, 1H, J = 7.8 Hz), 7.80 (td, 1H, J_1 = 7.7, J_2 = 1.7 Hz), 7.42-7.32 (m, 5H), 7.27-7.23 (m, 1H), 5.36-5.29 (m, 1H), 1.62 (d, 3H, J = 7.0 Hz).

$^{13}C\{^1H\}$ NMR (~101 MHz, $CDCl_3$): δ = 163.3, 149.8, 147.9, 143.2, 137.3, 128.6, 127.2, 126.1, 126.1, 122.2, 48.7, 22.0.

$[\alpha]^{25}_D$ = 8.20 (*c* = 0.10, DCM).

The enantiomeric excess (*ee* 99%) of compound **3a**-(*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 = 19.62 min, t_S = 30.11 min.

***N*-(1-(*p*-Tolyl)ethyl)picolinamide (3b-(*RS*)):**[11a]



The compound **3b**-(*RS*) was obtained as a colourless solid (311 mg, 65%, 2.0 mmol scale).

R_f = 0.6 (EtOAc:hexane = 20:80); mp: 90-92 ^oC.

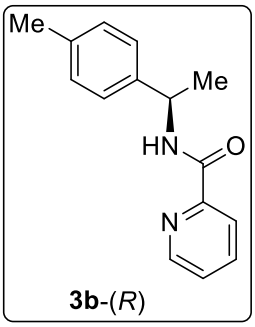
IR (DCM): 3384, 1673, 1512 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 8.52-8.51 (m, 1H), 8.30 (d, 1H, J = 7.2 Hz), 8.19 (dt, 1H, J_1 = 7.8, J_2 = 1.0 Hz), 7.82 (td, 1H, J_1 = 7.7, J_2 = 1.7 Hz), 7.41-7.38 (m, 1H), 7.30 (d, 2H, J = 8.1 Hz), 7.15 (d, 2H, J = 7.9 Hz), 5.32-5.25 (m, 1H), 2.32 (s, 3H), 1.61 (d, 3H, J = 6.9 Hz).

$^{13}C\{^1H\}$ NMR (~101 MHz, $CDCl_3$): δ = 163.3, 149.9, 147.9, 140.3, 137.3, 136.9, 129.3, 126.1, 126.1, 122.2, 48.5, 22.0, 21.0.

The HPLC of compound **3b**-(*RS*) was determined by using the Daicel Chiralpak IC column, hexane/*i*-PrOH 60:40, flow rate 1.0 mL/min, UV detection at 254 nm, t_R = 8.12 min, t_S = 12.50 min.

(*R*)-*N*-(1-(*p*-Tolyl)ethyl)picolinamide (3b-(*R*)):[17]



The compound **3b**-(*R*) was obtained as a colourless solid (304 mg, 63%, 2.0 mmol scale).

R_f = 0.6 (EtOAc/hexane = 20:80); mp: 90-92 °C.

IR (DCM): 3388, 1673, 1514 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 8.51 (d, 1H, J = 4.2 Hz), 8.31 (d, 1H, J = 7.3 Hz), 8.19 (d, 1H, J = 7.8 Hz), 7.81 (td, 1H, J_1 = 7.7, J_2 = 1.7 Hz), 7.40-7.37 (m, 1H), 7.30 (d, 2H, J = 8.0 Hz), 7.15 (d, 2H, J = 8.0 Hz), 5.33-5.25 (m, 1H), 2.32 (s, 3H), 1.61 (d, 3H, J = 6.9 Hz).

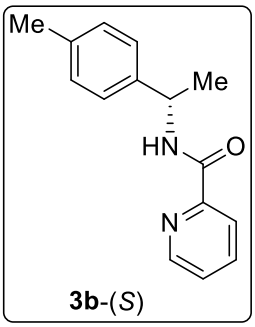
$^{13}C\{^1H\}$ NMR (~101 MHz, $CDCl_3$): δ = 163.2, 149.9, 147.9, 140.2, 137.2, 136.8, 129.2, 126.1, 126.0, 122.2, 48.5, 22.0, 21.0.

HRMS (ESI): *m/z* $[M+H]^+$ calcd for $C_{15}H_{17}N_2O$: 241.1341; found 241.1340.

$[\alpha]^{25}_D$ = -6.31 (c = 0.10, DCM).

The enantiomeric excess (*ee* 97%) of compound **3b**-(*R*) was determined by HPLC using the Daicel Chiralpak IC column, hexane/*i*-PrOH 60:40, flow rate 1.0 mL/min, UV detection at 254 nm, t_R = 8.10 min, t_S = 12.48 min.

(*S*)-*N*-(1-(*p*-Tolyl)ethyl)picolinamide (3b-(*S*)):



The compound **3b**-(*S*) was obtained as a colourless solid (311 mg, 65%, 2.0 mmol scale).

R_f = 0.6 (EtOAc/hexane = 20:80); mp: 90-92 °C.

IR (DCM): 3376, 1672, 1513 cm^{-1}.

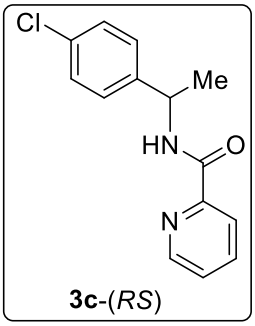
^1H NMR (400 MHz, $CDCl_3$): δ = 8.51 (d, 1H, J = 4.6 Hz), 8.30 (d, 1H, J = 7.0 Hz), 8.19 (d, 1H, J = 7.8 Hz), 7.82 (td, 1H, J_1 = 7.7, J_2 = 1.6 Hz), 7.42-7.38 (m, 1H), 7.30 (d, 2H, J = 8.0 Hz), 7.16 (d, 2H, J = 7.9 Hz), 5.32-5.25 (m, 1H), 2.33 (s, 3H), 1.61 (d, 3H, J = 6.9 Hz).

$^{13}C\{^1H\}$ NMR (~101 MHz, $CDCl_3$): δ = 163.3, 150.0, 148.0, 140.3, 137.3, 137.0, 129.3, 126.2, 126.1, 122.3, 48.6, 22.1, 21.1.

$[\alpha]^{25}_D$ = 9.22 (c = 0.10, DCM).

The enantiomeric excess (*ee* 99%) of compound **3b**-(*S*) was determined by HPLC using the Daicel Chiralpak IC column, hexane/*i*-PrOH 60:40, flow rate 1.0 mL/min, UV detection at 254 nm, t_R = 8.08 min, t_S = 12.46 min.

***N*-(1-(4-Chlorophenyl)ethyl)picolinamide (3c-(*RS*)):**



3c-(*RS*)

The compound **3c**-(*RS*) was obtained as a colourless solid (215 mg, 83%, 1.0 mmol scale).

R_f = 0.5 (EtOAc/hexane = 20:80); mp: 118-120 ºC.

IR (DCM): 3353, 1654, 1514 cm^{-1}.

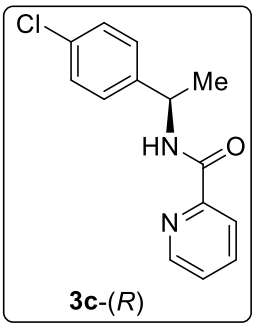
^1H NMR (500 MHz, $CDCl_3$): δ = 8.46 (d, 1H, J = 4.2 Hz), 8.21 (d, 1H, J = 5.5 Hz), 8.10 (d, 1H, J = 7.7 Hz), 7.76 (t, 1H, J = 7.6 Hz), 7.34 (t, 1H, J = 6.2 Hz), 7.27-7.19 (m, 4H), 5.23-5.17 (m, 1H), 1.52 (d, 3H, J = 6.8 Hz).

$^{13}C\{^1H\}$ NMR (~75 MHz, $CDCl_3$): δ = 163.4, 149.7, 148.0, 141.9, 137.3, 132.9, 128.7, 127.6, 126.2, 122.3, 48.2, 22.0.

HRMS (ESI): *m/z* $[M+H]^+$ calcd for $C_{14}H_{14}ClN_2O$: 261.0795; found: 261.0786.

The HPLC of compound **3c**-(*RS*) was determined using the Daicel Chiralpak IC column, hexane/*i*-PrOH 80:20, flow rate 1.0 mL/min, UV detection at 254 nm, t_R = 10.90 min, t_S = 15.28 min.

(*R*)-*N*-(1-(4-Chlorophenyl)ethyl)picolinamide (3c-(*R*)):[11a]



3c-(*R*)

The compound **3c**-(*R*) was obtained as a colourless solid (445 mg, 85%, 2.0 mmol scale).

R = 0.5 (EtOAc/hexane = 20:80); mp: 118-120 ºC.

IR (DCM): 3374, 1654, 1514 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 8.53 (d, 1H, J = 4.7 Hz), 8.32 (d, 1H, J = 7.3 Hz), 8.18 (d, 1H, J = 7.8 Hz), 7.83 (td, 1H, J_1= 7.7 Hz, $J_{2=}$ 1.5 Hz), 7.44-7.41 (m, 1H), 7.35-7.29 (m, 4H), 5.32-5.24 (m, 1H), 1.60 (d, 3H, J = 7.0 Hz).

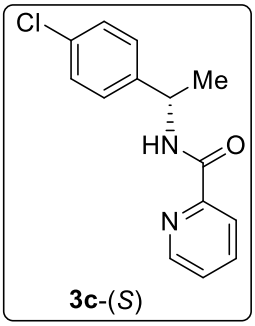
$^{13}C\{^1H\}$ NMR (~101 MHz, $CDCl_3$): δ = 163.5, 149.7, 148.1, 141.9, 137.4, 133.0, 128.8, 127.6, 126.3, 122.3, 48.3, 22.1.

HRMS (ESI): *m/z* $[M + Na]^+$ calcd for $C_{14}H_{13}ClN_2NaO$: 283.0614; found: 283.0623.

$[\alpha]^{25}_D$ = -10.18 (*c* = 0.10, DCM).

The enantiomeric excess (*ee* 95%) of compound **3c**-(*R*) was determined by HPLC using the Daicel Chiralpak IC column, hexane/*i*-PrOH 80:20, flow rate 1.0 mL/min, UV detection at 254 nm, t_R = 10.99 min, t_S = 15.39 min.

(*S*)-*N*-(1-(4-Chlorophenyl)ethyl)picolinamide (3c-(*S*)):



The compound **3c**-(*S*) was obtained as a colourless solid (430 mg, 83%, 2.0 mmol scale).

R_f = 0.5 (EtOAc/hexane = 20:80); mp: 117-119 ^oC.

IR (DCM): 3354, 1654, 1514 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 8.53 (d, 1H, J = 4.7 Hz), 8.32 (d, 1H, J = 7.2 Hz), 8.18 (d, 1H, J = 7.8 Hz), 7.83 (td, 1H, J_1= 7.7 Hz, $J_{2=}$ 1.6 Hz), 7.44-7.40 (m, 1H), 7.35-7.29 (m, 4H), 5.32-5.24 (m, 1H), 1.60 (d, 3H, J = 7.0 Hz).

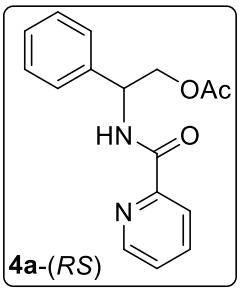
$^{13}C\{^1H\}$ NMR (~101 MHz, $CDCl_3$): δ = 163.5, 149.7, 148.1, 141.9, 137.4, 133.0, 128.8, 127.6, 126.3, 122.3, 48.3, 22.1.

HRMS (ESI): *m/z* $[M+H]^+$ calcd for $C_{14}H_{14}ClN_2O$: 261.0795; found: 261.0782.

$\alpha]^{25}_D$ = 15.23 (*c* = 0.10, DCM).

The enantiomeric excess (*ee* 95%) of compound **3c**-(*S*) was determined by HPLC using the Daicel Chiralpak IC column, hexane/*i*-PrOH 80:20, flow rate 1.0 mL/min, UV detection at 254 nm, t_R = 10.83 min, t_S = 15.10 min.

2-Phenyl-2-(picolinamido)ethyl acetate (4a-(*RS*)):



The compound **4a**-(*RS*) was obtained (from procedures A and B) as a colourless solid (1.19 g, 84%, 5 mmol scale).

R_f = 0.50 (EtOAc/hexane = 50:50); mp: 88-90 ^oC.

IR (DCM): 3374, 1740, 1518 cm^{-1}.

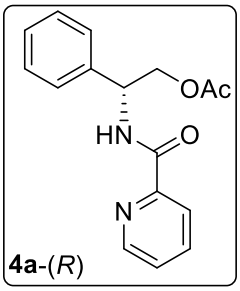
^1H NMR (400 MHz, $CDCl_3$): δ = 8.65 (d, 1H, J = 8.1 Hz), 8.59 (d, 1H, J = 4.3 Hz), 8.20 (d, 1H, J = 7.8 Hz), 7.85 (t, 1H, J = 7.6 Hz), 7.46-7.29 (m, 6H), 5.55-5.50 (m, 1H), 4.54-4.43 (m, 2H), 2.06 (s, 3H).

$^{13}C\{^1H\}$ NMR (~101 MHz, $CDCl_3$): δ = 170.9, 164.0, 149.5, 148.2, 138.4, 137.4, 128.8, 128.0, 126.8, 126.4, 122.4, 66.3, 52.3, 20.9.

HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{16}H_{17}N_2O_3$: 285.1239; found: 285.1230.

The HPLC of compound **4a**-(*RS*) was determined using the Daicel Chiralpak IC column, hexane/*i*-PrOH 80:20, flow rate 1.0 mL/min, UV detection at 254 nm, t_s = 25.88 min, t_R = 29.39 min.

(*R*)-2-Phenyl-2-(picolinamido)ethyl acetates (4a-(*R*)):



The compound **4a**-(*R*) was obtained (from procedures A and B) as a colourless solid (1.15 g, 81%, 5 mmol scale).

R_f = 0.50 (EtOAc/hexane = 50:50); mp: 88-90 ºC.

IR (DCM): 3369, 1740, 1517 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.65 (d, 1H, J = 8.3 Hz), 8.59 (d, 1H, J = 4.6 Hz), 8.20 (d, 1H, J = 7.8 Hz), 7.85 (td, 1H, J_1 = 7.7 Hz, J_2 = 1.2 Hz), 7.46-7.29 (m, 6H), 5.55-5.50 (m, 1H), 4.54-4.43 (m, 2H), 2.05 (s, 3H).

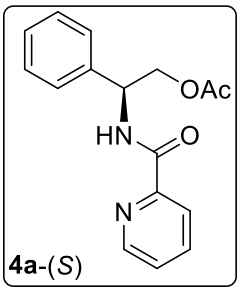
^{13}C{^{1}H} NMR (~101 MHz, $CDCl_3$): δ = 170.9, 163.9, 149.5, 148.2, 138.4, 137.4, 128.8, 128.0, 126.8, 126.4, 122.4, 66.3, 52.3, 20.9.

HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{16}H_{17}N_2O_3$: 285.1239; found: 285.1225.

$[\alpha]^{25}_D$ = 19.6 (c = 0.1, $CHCl_3$).

The enantiomeric excess (*ee* 98%) of compound **4a**-(*R*) was determined by HPLC using the Daicel Chiralpak IC column, hexane/*i*-PrOH 80:20, flow rate 1.0 mL/min, UV detection at 254 nm, t_s = 24.78 min, t_R = 29.64 min.

(*S*)-2-Phenyl-2-(picolinamido)ethyl acetate (4a-(*S*)):



The compound **4a**-(*S*) was obtained (from procedures A and B) as a colourless solid (1.16 g, 82%, 5 mmol scale).

R_f = 0.50 (EtOAc/hexane = 50:50); mp: 88-90 ºC.

IR (DCM): 3370, 1739 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.65 (d, 1H, J = 8.1 Hz), 8.59 (d, 1H, J = 4.3 Hz), 8.20 (d, 1H, J = 7.8 Hz), 7.86 (t, 1H, J = 7.6 Hz), 7.47-7.28 (m, 6H), 5.55-5.50 (m, 1H), 4.54-4.43 (m, 2H), 2.06 (s, 3H).

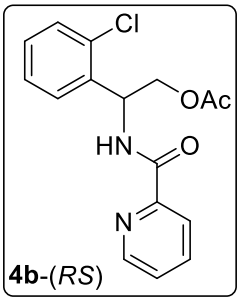
^{13}C{^{1}H} NMR (~101 MHz, $CDCl_3$): δ = 171.0, 164.0, 149.5, 148.2, 138.4, 137.4, 128.8, 128.0, 126.8, 126.4, 122.4, 66.3, 52.3, 20.9.

HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{16}H_{17}N_2O_3$: 285.1239; found: 285.1233.

$[\alpha]^{25}_D$ = -11.2 (c = 0.1, $CHCl_3$).

The enantiomeric excess (*ee* 98%) of compound **4a**-(*S*) was determined by HPLC using the Daicel Chiralpak IC column, hexane/*i*-PrOH 80:20, flow rate 1.0 mL/min, UV detection at 254 nm, t_s = 25.03, min t_R = 28.94 min.

2-(2-Chlorophenyl)-2-(picolinamido)ethyl acetate (4b-(*RS*)):



The compound **4b**-(*RS*) was obtained (from procedures A and B) as a yellow coloured semi-solid (527 mg, 83%, 2 mmol scale).

R_f = 0.55 (EtOAc/hexane = 50:50).

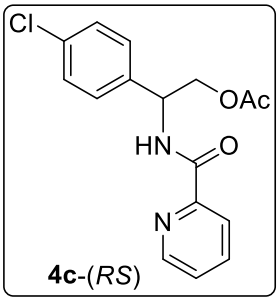
IR (DCM): 3370, 1741, 1513 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 8.84 (d, 1H, J = 8.0 Hz), 8.63 (d, 1H, J = 4.6 Hz), 8.19 (d, 1H, J = 7.8 Hz), 7.87 (t, 1H, J = 7.7 Hz), 7.49-7.40 (m, 3H), 7.27-7.25 (m, 2H), 5.89-5.85 (m, 1H), 4.59 (dd, 1H, J_1 = 11.5 Hz, J_2 = 7.0 Hz), 4.44 (dd, 1H, J_1 = 11.5 Hz, J_2 = 4.4 Hz), 2.07 (s, 3H).

$^{13}C\{^1H\}$ NMR (~101 MHz, $CDCl_3$): δ = 170.9, 163.9, 149.4, 148.3, 137.4, 135.8, 133.1, 130.0, 129.2, 128.1, 127.1, 126.5, 122.3, 64.9, 50.3, 20.8.

HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{16}H_{16}ClN_2O_3$: 319.0849; found: 319.0838.

2-(4-Chlorophenyl)-2-(picolinamido)ethyl acetate (4c-(*RS*)):



The compound **4c**-(*RS*) was obtained (from procedures A and B) as a yellow coloured semi-solid (540 mg, 85%, 2 mmol scale).

R_f = 0.55 (EtOAc/hexane = 50:50).

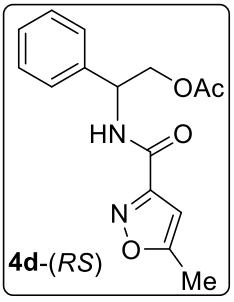
IR (DCM): 3364, 1738, 1510 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 8.68 (d, 1H, J = 8.2 Hz), 8.49 (d, 1H, J = 4.0 Hz), 8.12 (d, 1H, J = 7.8 Hz), 7.76 (t, 1H, J = 7.7 Hz), 7.38-7.24 (m, 5H), 5.46-5.41 (m, 1H), 4.46-4.35 (m, 2H), 1.98 (s, 3H).

$^{13}C\{^1H\}$ NMR (~101 MHz, $CDCl_3$): δ = 170.8, 164.0, 149.3, 148.2, 137.4, 137.1, 133.6, 128.8, 128.2, 126.5, 122.3, 66.0, 51.9, 20.7.

HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{16}H_{16}ClN_2O_3$: 319.0849; found: 319.0838.

2-(5-Methylisoxazole-3-carboxamido)-2-phenylethyl acetate (4d- (*RS*)):



The compound **4d**-(*RS*) was obtained (from procedures A and B) as a colourless solid (328 mg, 57%, 2 mmol scale).

R_f = 0.50 (EtOAc/hexane = 50:50); mp: 124-126 ^oC.

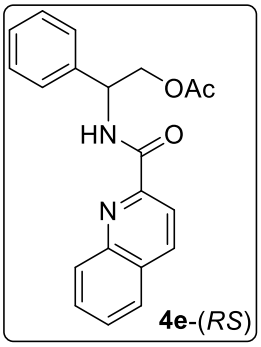
IR (DCM): 3379, 1741, 1544 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.45 (d, 1H, J = 8.1 Hz), 7.38-7.35 (m, 4H), 7.34-7.30 (m, 1H), 6.44 (s, 1H), 5.49-5.44 (m, 1H), 4.48-4.39 (m, 2H), 2.48 (s, 3H), 2.06 (s, 3H).

$^{13}C\{^1H\}$ NMR (~101 MHz, $CDCl_3$): δ = 171.4, 171.0, 158.8, 158.5, 137.7, 128.9, 128.2, 126.7, 101.5, 66.0, 52.4, 20.8, 12.4.

HRMS (ESI): *m/z* $[M + Na]^+$ calcd for $C_{15}H_{16}N_2NaO_4$: 311.1008; found: 311.0995.

2-Phenyl-2-(quinoline-2-carboxamido)ethyl acetate (4e-(*RS*)):



The compound **4e**-(*RS*) was obtained (from procedures A and B) as a colourless solid (541 mg, 81%, 2 mmol scale).

R_f = 0.55 (EtOAc/hexane = 50:50); mp: 104-106 °C.

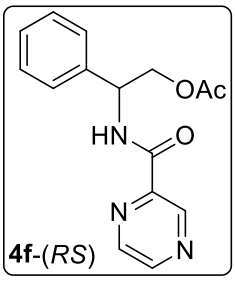
IR (DCM): 3372, 1738, 1372 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 8.87 (d, 1H, J = 8.4 Hz), 8.33 (s, 2H), 8.18 (d, 1H, J = 8.5 Hz), 7.90 (d, 1H, J = 8.2 Hz), 7.80 (t, 1H, J = 7.2 Hz), 7.64 (t, 1H, J = 7.6 Hz), 7.49 (d, 2H, J = 7.7 Hz), 7.43-7.39 (m, 2H), 7.35-7.32 (m, 1H), 5.62-5.57 (m, 1H), 4.62-4.50 (m, 2H), 2.10 (s, 3H).

$^{13}C\{^1H\}$ NMR (~101 MHz, $CDCl_3$): δ = 171.1, 164.2, 149.4, 146.5, 138.4, 137.6, 130.2, 129.9, 129.4, 128.9, 128.1, 128.0, 127.8, 126.9, 118.9, 66.3, 52.5, 20.9.

HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{20}H_{19}N_2O_3$: 335.1396; found: 335.1390.

2-Phenyl-2-(pyrazine-2-carboxamido)ethyl acetate (4f-(*RS*)):



The compound **4f**-(*RS*) was obtained (from procedures A and B) as a colourless solid (467 mg, 82%, 2 mmol scale).

R_f = 0.55 (EtOAc/hexane = 50:50); mp: 150-152 °C.

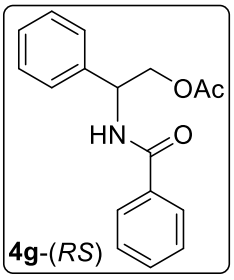
IR (DCM): 3373, 1741, 1518 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 9.40 (s, 1H), 8.76 (s, 1H), 8.56 (s, 1H), 8.42 (d, 1H, J = 8.2 Hz), 7.41-7.29 (m, 5H), 5.54-5.49 (m, 1H), 4.52 (dd, 1H, J_1 = 11.5 Hz, J_2 = 7.5 Hz), 4.43 (dd, 1H, J_1 = 11.6 Hz, J_2 = 4.6 Hz), 2.05 (s, 3H).

$^{13}C\{^1H\}$ NMR (~101 MHz, $CDCl_3$): δ = 171.0, 162.7, 147.5, 144.5, 144.1, 142.7, 137.9, 128.9, 128.2, 126.8, 66.1, 52.5, 20.8.

HRMS (ESI): *m/z* $[M + Na]^+$ calcd for $C_{15}H_{15}N_3NaO_3$: 308.1011; found: 308.1019.

2-Benzamido-2-phenylethyl acetate (4g-(*RS*)):



The compound **4g**-(*RS*) was obtained (from procedures A and B) as a colourless solid (240 mg, 85%, 1 mmol scale).

R_f = 0.50 (EtOAc/hexane = 50:50); mp: 126-128 °C.

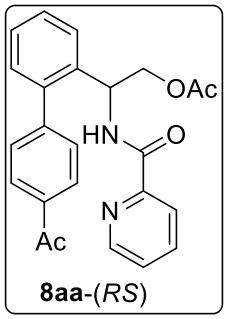
IR (DCM): 1741, 1638 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.82 (d, 2H, J = 7.6 Hz), 7.53 (t, 1H, J = 7.2 Hz), 7.47-7.43 (m, 2H), 7.39-7.32 (m, 5H), 7.04 (d, 1H, J = 7.0 Hz), 5.52-5.47 (m, 1H), 4.62 (dd, 1H, J_1 = 11.4 Hz, J_2 = 8.3 Hz), 4.34 (dd, 1H, J_1 = 11.6 Hz, J_2 = 4.1 Hz), 2.08 (s, 3H).

$^{13}C\{^1H\}$ NMR (~101 MHz, $CDCl_3$): δ = 171.8, 167.0, 138.3, 134.0, 131.7, 128.9, 128.6, 128.0, 127.1, 126.7, 66.2, 53.5, 20.9.

HRMS (ESI): *m/z* $[M + Na]^+$ calcd for $C_{17}H_{17}NNaO_3$: 306.1106; found: 306.1111.

2-(4'-Acetyl-[1,1'-biphenyl]-2-yl)-2-(picolinamido)ethyl acetate (8aa-(*RS*)):



8aa-(*RS*)

The racemic compound **8aa**-(*RS*) (from **4a**-(*RS*) under the optimized condition using $Pd(OAc)_2$, KOAc condition) was obtained as a colourless semi-solid (28 mg, 35%, 0.2 mmol scale).

R_f = 0.35 (EtOAc/hexane = 50:50).

IR (DCM): 3367, 1751, 1505 cm^{-1}.

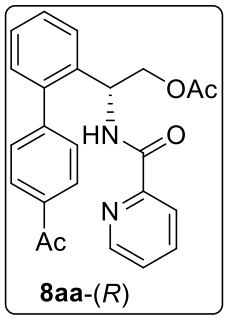
^1H NMR (400 MHz, $CDCl_3$): δ = 8.71 (d, 1H, *J* = 7.7 Hz), 8.60 (d, 1H, *J* = 4.2 Hz), 8.15 (d, 1H, *J* = 7.8 Hz), 8.08 (d, 2H, *J* = 7.9 Hz), 7.85 (t, 1H, *J* = 7.7 Hz), 7.65 (d, 2H, *J* = 7.8 Hz), 7.55 (d, 1H, *J* = 7.6 Hz), 7.48-7.36 (m, 3H), 7.25 (d, 1H, *J* = 7.4 Hz), 5.61-5.56 (m, 1H), 4.33 (dd, 1H, J_1 = 11.5 Hz, J_2 = 7.4 Hz), 4.12 (dd, 1H, J_1 = 11.5 Hz, J_2 = 4.5 Hz), 2.67 (s, 3H), 2.00 (s, 3H).

$^{13}C\{^1H\}$ NMR (~101 MHz, $CDCl_3$): δ = 197.9, 170.9, 163.9, 149.4, 148.2, 145.5, 140.7, 137.4, 136.1, 136.0, 130.2, 129.7, 128.6, 128.4, 127.9, 126.4, 126.4, 122.2, 65.9, 49.7, 26.7, 20.8.

HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{24}H_{23}N_2O_4$: 403.1658; found: 403.1646.

The HPLC of compound **8aa**-(*RS*) was determined by using the Daicel Chiralpak IA column, hexane/*i*-PrOH 80:20, flow rate 1.0 mL/min, UV detection at 254 nm, t_S = 11.01 min, t_R = 11.95 min.

(*R*)-2-(4'-Acetyl-[1,1'-biphenyl]-2-yl)-2-(picolinamido)ethyl acetate (8aa-(*R*)):



8aa-(*R*)

The compound **8aa**-(*R*) (from **4a**-(*R*) under the optimized condition using $Pd(OAc)_2$, KOAc condition) was obtained as a colourless semi-solid (33 mg, 41%, 0.2 mmol scale).

R_f = 0.35 (EtOAc/hexane = 50:50).

IR (DCM): 3367, 1738, 1511 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 8.71 (d, 1H, *J* = 7.8 Hz), 8.60 (d, 1H, *J* = 4.5 Hz), 8.14 (d, 1H, *J* = 7.8 Hz), 8.08 (d, 2H, *J* = 8.3 Hz), 7.85 (td, 1H, J_1 = 7.7 Hz, J_2 = 1.2 Hz), 7.65 (d, 2H, *J* = 8.0 Hz), 7.55 (d, 1H, *J* = 7.5 Hz), 7.47-7.35 (m, 3H), 7.25 (d, 1H, *J* = 7.3 Hz), 5.61-5.56 (m, 1H), 4.36-4.31 (m, 1H), 4.13 (dd, 1H, J_1 = 11.5 Hz, J_2 = 4.6 Hz), 2.67 (s, 3H), 2.00 (s, 3H).

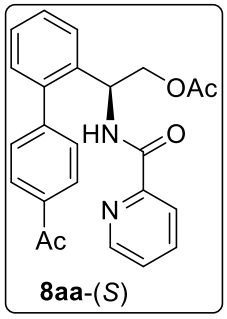
$^{13}C\{^1H\}$ NMR (~101 MHz, $CDCl_3$): δ = 197.9, 170.9, 163.9, 149.4, 148.2, 145.5, 140.7, 137.4, 136.1, 136.0, 130.2, 129.7, 128.6, 128.4, 127.9, 126.4, 126.4, 122.2, 65.9, 49.7, 26.8, 20.8.

HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{24}H_{23}N_2O_4$: 403.1658; found: 403.1642.

$[\alpha]^{25}_D$ = 175.9 (*c* = 0.06, $CHCl_3$).

The enantiomeric excess (*ee* 96%) of compound **8aa**-(*R*) 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_S = 11.48 min, t_R = 12.14 min.

(*S*)-2-(4'-Acetyl-[1,1'-biphenyl]-2-yl)-2-(picolinamido)ethyl acetate (8aa-(*S*)):



8aa-(*S*)

The compound **8aa**-(*S*) (from **4a**-(*S*) under the optimized condition using $Pd(OAc)_2$, KOAc condition) was obtained as a colourless semi-solid (30 mg, 37%, 0.2 mmol scale).

R_f = 0.35 (EtOAc/hexane = 50:50).

IR (DCM): 3367, 1751, 1505 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 8.71 (d, 1H, *J* = 7.6 Hz), 8.60 (d, 1H, *J* = 4.6 Hz), 8.15 (d, 1H, *J* = 7.8 Hz), 8.08 (d, 2H, *J* = 7.8 Hz), 7.85 (t, 1H, *J* = 7.7 Hz), 7.65 (d, 2H, *J* = 7.8 Hz), 7.55 (d, 1H, *J* = 7.6 Hz), 7.48-7.35 (m, 3H), 7.25 (d, 1H, *J* = 7.4 Hz), 5.61-5.56 (m, 1H), 4.33 (dd, 1H, J_1 = 11.3 Hz, J_2 = 7.4 Hz), 4.12 (dd, 1H, J_1 = 11.4 Hz, J_2 = 4.5 Hz), 2.67 (s, 3H), 2.00 (s, 3H).

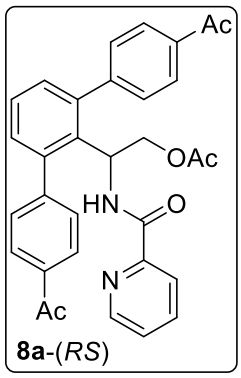
$^{13}C\{^1H\}$ NMR (~101 MHz, $CDCl_3$): δ = 197.9, 170.9, 163.9, 149.4, 148.2, 145.5, 140.7, 137.4, 136.1, 136.0, 130.2, 129.7, 128.6, 128.4, 127.9, 126.4, 126.4, 122.2, 65.9, 49.7, 26.7, 20.8.

HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{24}H_{23}N_2O_4$: 403.1658; found: 403.1648.

$[\alpha]^{25}_D$ = -170.5 (*c* = 0.06, $CHCl_3$).

The enantiomeric excess (*ee* 95%) of compound **8aa**-(*S*) 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_S = 10.20 min, t_R = 10.92 min.

2-(4,4''-Diacetyl-[1,1':3',1''-terphenyl]-2'-yl)-2-(picolinamido)ethyl acetate (8a-(*RS*)):



8a-(*RS*)

The compound **8a**-(*RS*) was obtained as a colourless solid (89 mg, 86%, 0.2 mmol scale).

R_f = 0.35 (EtOAc/hexane = 50:50); mp: 104-106 °C.

IR (DCM): 3371, 1740, 1511 cm^{-1}.

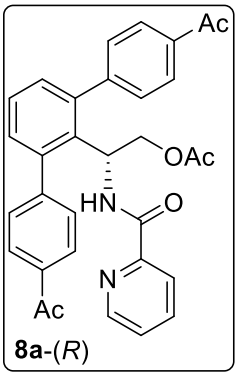
^1H NMR (400 MHz, $CDCl_3$): δ = 8.31 (d, 1H, *J* = 4.6 Hz), 8.05-7.34 (m, 13H), 7.18 (d, 2H, *J* = 7.6 Hz), 5.68-5.62 (m, 1H), 4.27-4.22 (m, 1H), 4.14 (dd, 1H, J_1 = 11.5 Hz, J_2 = 4.9 Hz), 2.67 (s, 6H), 1.88 (s, 3H).

$^{13}C\{^1H\}$ NMR (~101 MHz, $CDCl_3$): δ = 197.8, 170.6, 163.4, 149.0, 147.8, 146.6, 141.8, 137.2, 136.1, 132.9, 130.8, 130.0, 128.4, 127.1, 126.3, 121.9, 65.8, 50.5, 26.8, 20.7.

HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{32}H_{29}N_2O_5$: 521.2076; found: 521.2058.

The HPLC of compound **8a**-(*RS*) was determined by using the Daicel Chiralpak IA column, hexane/*i*-PrOH 80:20, flow rate 1.0 mL/min, UV detection at 254 nm, t_S = 13.44 min, t_R = 15.05 min.

(*R*)-2-(4,4''-Diacetyl-[1,1':3',1''-terphenyl]-2'-yl)-2-(picolinamido)ethyl acetate (8a-(*R*)):



8a-(*R*)

The compound **8a**-(*R*) was obtained as a colourless solid (100 mg, 96%, 0.2 mmol scale).

R_f = 0.35 (EtOAc/hexane = 50:50); mp: 104-106 °C.

IR (DCM): 3371, 1742, 1513 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ 8.31-8.30 (m, 1H), 8.04-7.33 (m, 13H), 7.17 (d, 2H, J = 7.6 Hz), 5.67-5.62 (m, 1H), 4.26-4.21 (m, 1H), 4.13 (dd, 1H, J_1 = 11.5 Hz, J_2 = 5.0 Hz), 2.65 (s, 6H), 1.86 (s, 3H).

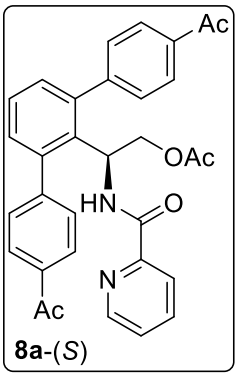
$^{13}C\{^1H\}$ NMR (~101 MHz, $CDCl_3$): δ 197.7, 170.6, 163.4, 149.0, 147.8, 146.5, 141.8, 137.2, 136.1, 132.9, 130.7, 129.8, 128.3, 127.0, 126.2, 121.9, 65.8, 50.5, 26.7, 20.7.

HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{32}H_{29}N_2O_5$: 521.2076; found: 521.2056.

$[\alpha]^{25}_D$ = 119.5 (c = 0.04, $CHCl_3$).

The enantiomeric excess (*ee* >97%) of compound **8a**-(*R*) 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_S = 13.03 min, t_R = 14.30.

(*S*)-2-(4,4''-Diacetyl-[1,1':3',1''-terphenyl]-2'-yl)-2-(picolinamido)ethyl acetate (8a-(*S*)):



8a-(*S*)

The compound **8a**-(*S*) was obtained as a colourless solid (79 mg, 76%, 0.2 mmol scale).

R_f = 0.35 (EtOAc/hexane = 50:50); mp: 104-106 °C.

IR (DCM): 3367, 1738, 1510 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 8.32 (d, 1H, J = 4.6 Hz), 8.06-7.34 (m, 13H), 7.17 (d, 2H, J = 7.6 Hz), 5.67-5.64 (m, 1H), 4.27-4.12 (m, 2H), 2.67 (s, 6H), 1.88 (s, 3H).

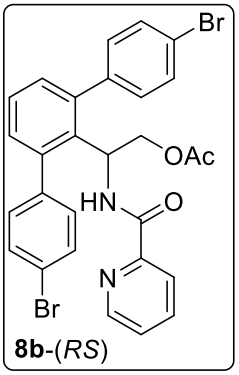
$^{13}C\{^1H\}$ NMR (~101 MHz, $CDCl_3$): δ = 197.8, 170.6, 163.4, 149.0, 147.8, 146.6, 141.8, 137.2, 136.1, 132.9, 130.7, 129.8, 128.4, 127.0, 126.3, 121.9, 65.8, 50.5, 26.7, 20.7.

HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{32}H_{29}N_2O_5$: 521.2076; found: 521.2064.

$[\alpha]^{25}_D$ = -127.0 (c = 0.04, $CHCl_3$).

The enantiomeric excess (*ee* >98%) of compound **8a**-(*S*) 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_S = 12.76 min, t_R = 14.44.

2-(4,4''-Dibromo-[1,1':3',1''-terphenyl]-2'-yl)-2-(picolinamido)ethyl acetate (8b-(*RS*)):



The compound **8b**-(*RS*) was obtained as a yellow coloured solid (107 mg, 90%, 0.2 mmol scale).

R_f = 0.55 (EtOAc/hexane = 50:50); mp: 185-187 ^oC.

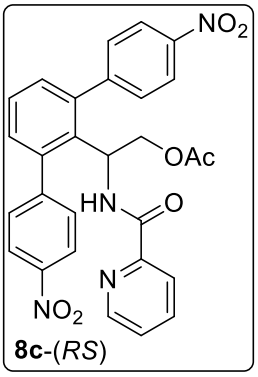
IR (DCM): 3298, 1672, 1351 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 8.50 (d, 1H, J = 4.5 Hz), 8.05 (d, 1H, J = 7.8 Hz), 7.82-7.79 (m, 2H), 7.63-7.15 (m, 12H), 5.72-5.66 (m, 1H), 4.28-4.23 (m, 1H), 4.17-4.13 (m, 1H), 1.93 (s, 3H).

$^{13}C\{^1H\}$ NMR (~101 MHz, $CDCl_3$): δ = 170.7, 163.4, 149.0, 148.0, 141.6, 140.5, 137.2, 133.2, 131.4, 131.1, 130.9, 127.0, 126.2, 121.8, 121.7, 66.0, 50.5, 20.8.

HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{28}H_{23}Br_2N_2O_3$: 593.0075; found:593.0099.

2-(4,4''-Dinitro-[1,1':3',1''-terphenyl]-2'-yl)-2-(picolinamido)ethyl acetate (8c-(*RS*)):



The compound **8c**-(*RS*) was obtained as a yellow coloured semi-solid (84 mg, 80%, 0.2 mmol scale).

R_f = 0.40 (EtOAc/hexane = 50:50).

IR (DCM): 3370, 1739, 1510 cm^{-1}.

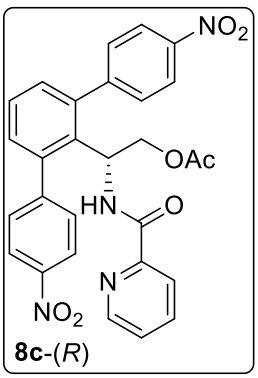
^1H NMR (400 MHz, $CDCl_3$): δ = 8.33-7.21 (m, 16H), 5.58-5.53 (m, 1H), 4.28-4.12 (m, 2H), 1.90 (s, 3H).

$^{13}C\{^1H\}$ NMR (~101 MHz, $CDCl_3$): δ = 170.5, 163.5, 148.6, 148.2, 147.9, 147.3, 140.8, 137.4, 132.9, 131.0, 130.5, 127.4, 126.6, 123.5, 121.9, 65.3, 50.8, 20.6.

HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{28}H_{23}N_4O_7$: 527.1567; found: 527.1589.

The HPLC of compound **8c**-(*RS*) was determined by using the Daicel Chiralpak AD-H column, hexane/*i*-PrOH 80:20, flow rate 1.0 mL/min, UV detection at 254 nm, t_S = 19.85 min, t_R = 26.06 min.

(*R*)-2-(4,4''-Dinitro-[1,1':3',1''-terphenyl]-2'-yl)-2-(picolinamido)ethyl acetate (8c-(*R*)):



The compound **8c**-(*R*) was obtained as a yellow coloured semi-solid (82 mg, 78%, 0.2 mmol scale).

R_f = 0.40 (EtOAc/hexane = 50:50).

IR (DCM): 3374, 1742, 1513 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 8.33-7.21 (m, 16H), 5.58-5.52 (m, 1H), 4.28-4.12 (m, 2H), 1.89 (s, 3H).

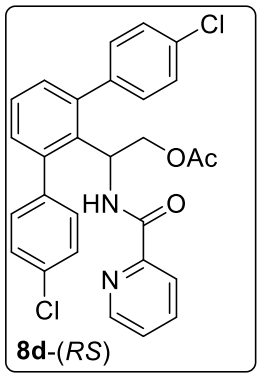
$^{13}C\{^1H\}$ NMR (~101 MHz, $CDCl_3$): δ = 170.6, 163.5, 148.6, 148.2, 147.9, 147.3, 140.8, 137.4, 132.9, 131.0, 130.5, 127.4, 126.6, 123.6, 121.9, 65.3, 50.8, 20.7.

HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{28}H_{23}N_4O_7$: 527.1567; found: 527.1585.

$[\alpha]^{25}_{D}$ = 135.3 (*c* = 0.06, $CHCl_3$).

The enantiomeric excess (*ee* 98%) of compound **8c**-(*R*) was determined by HPLC using the Daicel Chiralpak AD-H column, hexane/*i*-PrOH 80:20, flow rate 1.0 mL/min, UV detection at 254 nm, t_S = 22.43 min, t_R = 27.45 min.

2-(4,4''-Dichloro-[1,1':3',1''-terphenyl]-2'-yl)-2-(picolinamido)ethyl acetate (8d-(*RS*)):



8d-(*RS*)

The compound **8d**-(*RS*) was obtained as a colourless solid (75 mg, 75%, 0.2 mmol scale).

R_f = 0.65 (EtOAc/hexane = 50:50); mp: 127-129 ºC.

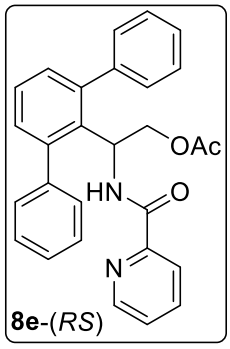
IR (DCM): 3374, 1741, 1505 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.48 (d, 1H, *J* = 4.0 Hz), 8.06 (d, 1H, *J* = 7.8 Hz), 7.82-7.79 (m, 2H), 7.57-7.15 (m, 12H), 5.72-5.66 (m, 1H), 4.28-4.13 (m, 2H), 1.91 (s, 3H).

^{13}C{^{1}H} NMR (~101 MHz, $CDCl_3$): δ = 170.7, 163.4, 149.1, 147.9, 141.6, 140.0, 137.1, 133.5, 133.4, 131.0, 130.8, 128.5, 127.0, 126.2, 121.8, 66.0, 50.5, 20.8.

HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{28}H_{23}Cl_2N_2O_3$: 505.1086; found: 505.1093.

2-([1,1':3',1''-Terphenyl]-2'-yl)-2-(picolinamido)ethyl acetate (8e-(*RS*)):



8e-(*RS*)

The compound **8e**-(*RS*) was obtained as a yellow coloured semi-solid (82 mg, 94%, 0.2 mmol scale).

R_f = 0.55 (EtOAc/hexane = 50:50).

IR (DCM): 3373, 1742, 1513 cm^{-1}.

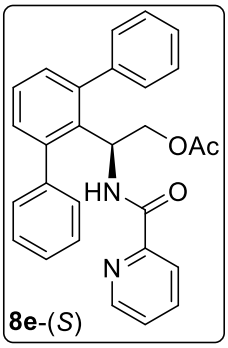
^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.43 (d, 1H, *J* = 4.4 Hz), 8.08 (d, 1H, *J* = 7.8 Hz), 7.90 (d, 1H, *J* = 8.9 Hz), 7.79 (t, 1H, *J* = 7.7 Hz), 7.58-7.18 (m, 14H), 5.79-5.74 (m, 1H), 4.30-4.16 (m, 2H), 1.88 (s, 3H).

^{13}C{^{1}H} NMR (~101 MHz, $CDCl_3$): δ = 170.7, 163.4, 149.5, 147.7, 142.9, 141.7, 137.0, 133.4, 130.7, 129.6, 128.2, 127.4, 126.7, 126.0, 121.8, 66.2, 50.4, 20.8.

HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{28}H_{25}N_2O_3$: 437.1865; found: 437.1854.

The HPLC of compound **8e**-(*RS*) was determined by using the Daicel Chiralcel OD column, hexane/*i*-PrOH 96:04, flow rate 0.5 mL/min, UV detection at 254 nm, t_S = 25.90 min, t_R = 29.35 min.

(*S*)-2-([1,1':3',1''-Terphenyl]-2'-yl)-2-(picolinamido)ethyl acetate (8e-(*S*)):



The compound **8e**-(*S*) was obtained as a yellow coloured semi-solid (76 mg, 87%, 0.2 mmol scale).

R_f = 0.65 (EtOAc/hexane = 50:50).

IR (DCM): 3370, 1738, 1509 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 8.43 (d, 1H, J = 4.6 Hz), 8.09 (d, 1H, J = 7.8 Hz), 7.91 (d, 1H, J = 9.0 Hz), 7.79 (t, 1H, J = 7.7 Hz), 7.49-7.18 (m, 14H), 5.80-5.74 (m, 1H), 4.28 (t, 1H, J = 10.8 Hz), 4.28 (t, 1H, J_1 = 11.5, J_2 = 4.88 Hz), 1.88 (s, 3H).

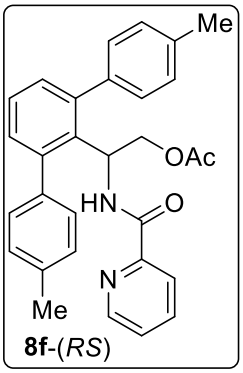
$^{13}C\{^1H\}$ NMR (~101 MHz, $CDCl_3$): δ = 170.7, 163.4, 149.5, 147.7, 142.9, 141.7, 137.0, 133.4, 130.7, 129.6, 128.2, 127.4, 126.7, 126.0, 122.0, 66.2, 50.4, 20.8.

HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{28}H_{25}N_2O_3$: 437.1865; found: 437.1846.

$[\alpha]^{25}_D$ = -47.2 (c = 0.05, $CHCl_3$).

The enantiomeric excess (*ee* 90%) of compound **8e**-(*S*) was determined by HPLC using the Daicel Chiralcel OD column, hexane/*i*-PrOH 96:04, flow rate 0.5 mL/min, UV detection at 254 nm, t_S = 25.55 min, t_R = 28.91 min.

2-(4,4''-Dimethyl-[1,1':3',1''-terphenyl]-2'-yl)-2-(picolinamido)ethyl acetate (8f-(*RS*)):



The compound **8f**-(*RS*) was obtained as a yellow coloured solid (73 mg, 79%, 0.2 mmol scale).

R_f = 0.55 (EtOAc/hexane = 50:50); mp: 80-82 °C.

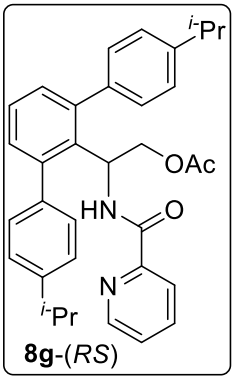
IR (DCM): 3372, 1741, 1512 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 8.44 (d, 1H, J = 4.7 Hz), 8.08 (d, 1H, J = 7.8 Hz), 7.94 (d, 1H, J = 9.1 Hz), 7.80 (td, 1H, J_1 = 7.7 Hz, J_2 = 1.0 Hz), 7.40-7.17 (m, 12H), 5.82-5.76 (m, 1H), 4.28-4.16 (m, 2H), 2.45 (s, 6H), 1.89 (s, 3H).

$^{13}C\{^1H\}$ NMR (~101 MHz, $CDCl_3$): δ = 170.8, 163.3, 149.6, 147.6, 142.9, 138.8, 137.0, 136.9, 133.6, 130.7, 129.4, 128.9, 126.6, 125.9, 122.0, 66.4, 50.3, 21.3, 20.8.

HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{30}H_{29}N_2O_3$: 465.2178; found: 465.2174.

2-(4,4''-Diisopropyl-[1,1':3',1''-terphenyl]-2'-yl)-2-(picolinamido)ethyl acetate (8g-(*RS*)):



The compound **8g**-(*RS*) was obtained as a yellow coloured semi-solid (65 mg, 63%, 0.2 mmol scale).

R_f = 0.65 (EtOAc/hexane = 50:50).

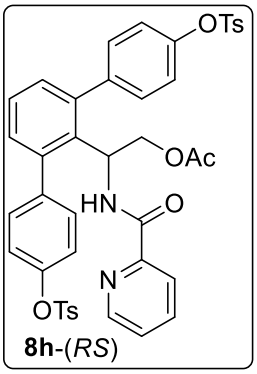
IR (DCM): 3371, 1740, 1511 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 8.41 (d, 1H, *J* = 4.4 Hz), 8.09 (d, 1H, *J* = 7.8 Hz), 7.88 (d, 1H, *J* = 8.6 Hz), 7.79 (t, 1H, *J* = 7.7 Hz), 7.39-7.26 (m, 10H), 7.19 (d, 1H, *J* = 7.4 Hz), 5.83-5.77 (m, 1H), 4.28-4.25 (m, 2H), 3.04-3.0 (m, 2H), 1.90 (s, 3H), 1.35 (d, 12H, *J* = 6.8 Hz).

$^{13}C\{^1H\}$ NMR (~101 MHz, $CDCl_3$): δ = 170.7, 163.4, 149.6, 147.7, 142.9, 139.1, 137.2, 137.0, 133.7, 130.8, 129.4, 126.6, 126.2, 125.9, 122.0, 66.6, 50.5, 30.8, 24.2, 20.8.

HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{34}H_{37}N_2O_3$: 521.2804; found: 521.2820.

2-(4,4''-Bis(tosyloxy)-[1,1':3',1''-terphenyl]-2'-yl)-2-(picolinamido)ethyl acetate (8h-(*RS*)):



The compound **8h**-(*RS*) was obtained as a colourless solid (105 mg, 68%, 0.2 mmol scale).

R_f = 0.45 (EtOAc/hexane = 50:50); mp: 174-176 ^oC.

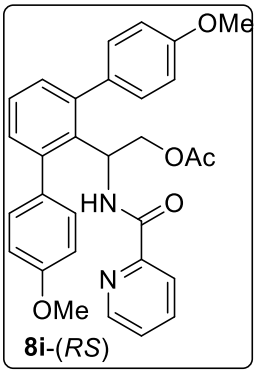
IR (DCM): 3374, 1743, 1506 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 8.54 (d, 1H, *J* = 4.3 Hz), 8.04 (d, 1H, *J* = 7.8 Hz), 7.83-7.78 (m, 6H), 7.44-7.13 (m, 12H), 7.05 (br. s, 4H), 5.61-5.56 (m, 1H),), 4.13-4.03 (m, 2H), 2.45 (s, 6H), 1.90 (s, 3H).

$^{13}C\{^1H\}$ NMR (~101 MHz, $CDCl_3$): δ = 170.4, 163.5, 149.0, 148.3, 145.4, 141.6, 140.4, 137.1, 133.5, 132.3, 131.0, 130.9, 130.8, 129.8, 126.9, 126.3, 122.2, 121.8, 65.9, 50.3, 21.7, 20.7.

HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{42}H_{37}N_2O_9S_2$: 777.1940; found: 777.1978.

2-(4,4''-Dimethoxy-[1,1':3',1''-terphenyl]-2'-yl)-2-(picolinamido)ethyl acetate (8i-(*RS*)):



The compound **8i**-(*RS*) was obtained as a yellow coloured semi-solid (79 mg, 80%, 0.2 mmol scale).

R_f = 0.40 (EtOAc/hexane = 50:50).

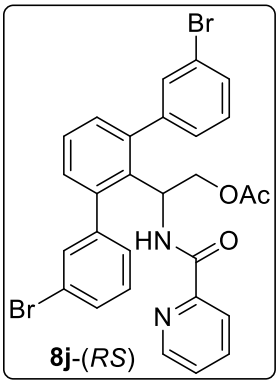
IR (DCM): 3363, 1743, 1505 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 8.45 (d, 1H, *J* = 4.4 Hz), 8.08 (d, 1H, *J* = 7.8 Hz), 7.97 (d, 1H, *J* = 9.1 Hz), 7.79 (td, 1H, J_1 = 7.7 Hz, J_2 = 1.4 Hz), 7.47-7.17 (m, 8H), 6.98 (br. s, 4H), 5.84-5.78 (m, 1H), 4.28-4.17 (m, 2H), 3.89 (s, 6H), 1.90 (s, 3H).

$^{13}C\{^{1}H\}$ NMR (~101 MHz, $CDCl_3$): δ = 170.8, 163.3, 158.9, 149.6, 147.7, 142.6, 137.0, 134.0, 134.0, 131.0, 130.6, 126.7, 126.0, 122.0, 113.6, 66.4, 55.3, 50.3, 20.8.

HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{30}H_{29}N_2O_5$: 497.2076; found: 497.2064.

2-(3,3''-Dibromo-[1,1':3',1''-terphenyl]-2'-yl)-2-(picolinamido)ethyl acetate (8j-(*RS*)):



8j-(*RS*)

The compound **8j**-(*RS*) was obtained as a yellow coloured semi-solid (98 mg, 83%, 0.2 mmol scale).

R_f = 0.60 (EtOAc/hexane = 50:50).

IR (DCM): 3376, 1743, 1511 cm^{-1}.

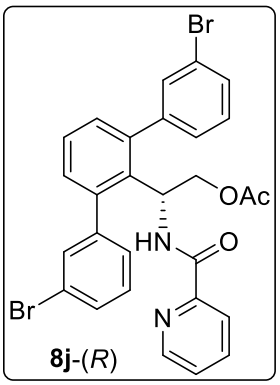
^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.52 (d, 1H, *J* = 0.5 Hz), 8.08 (d, 1H, *J* = 7.8 Hz), 7.89 (d, 1H, *J* = 8.6 Hz), 7.80 (t, 1H, *J* = 7.6 Hz), 7.56-7.17 (m, 12H), 5.70-5.65 (m, 1H), 4.29-4.16 (m, 2H), 1.95 (s, 3H).

$^{13}C\{^{1}H\}$ NMR (~101 MHz, $CDCl_3$): δ = 170.7, 163.4, 149.1, 148.4, 143.5, 141.4, 137.1, 133.4, 132.5, 131.0, 130.6, 129.7, 128.2, 126.9, 126.1, 122.5, 122.0, 66.0, 50.3, 20.8.

HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{28}H_{23}Br_2N_2O_3$: 593.0075; found: 593.0104.

The HPLC of compound **8j**-(*RS*) was determined by using the Daicel Chiralpak IA column, hexane/*i*-PrOH 80:20, flow rate 1.0 mL/min, UV detection at 254 nm, t_S = 8.58 min, t_R = 7.85 min.

(*R*)-2-(3,3''-Dibromo-[1,1':3',1''-terphenyl]-2'-yl)-2-(picolinamido)ethyl acetate (8j-(*R*)):



8j-(*R*)

The compound **8j**-(*R*) was obtained as a yellow coloured semi-solid (98 mg, 84%, 0.2 mmol scale).

R_f = 0.60 (EtOAc/hexane = 50:50).

IR (DCM): 3375, 1742, 1511 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.52 (s, 1H), 8.08 (d, 1H, *J* = 7.8 Hz), 7.90 (d, 1H, *J* = 8.5 Hz), 7.80 (t, 1H, *J* = 7.6 Hz), 7.56-7.17 (m, 12H), 5.70-5.65 (m, 1H), 4.29-4.16 (m, 2H), 1.94 (s, 3H).

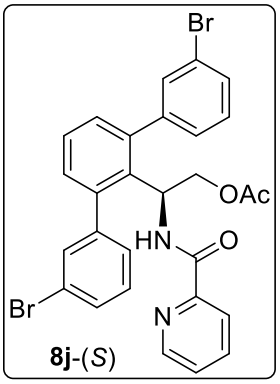
$^{13}C\{^{1}H\}$ NMR (~101 MHz, $CDCl_3$): δ = 170.7, 163.4, 149.1, 148.4, 143.5, 141.4, 137.1, 133.4, 132.5, 131.0, 130.6, 129.7, 128.2, 126.9, 126.1, 122.5, 122.0, 66.0, 50.3, 20.8.

HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{28}H_{23}Br_2N_2O_3$: 593.0075; found: 593.0046.

$[\alpha]^{25}_D$ = 105.3 (*c* = 0.06, $CHCl_3$).

The enantiomeric excess (*ee* 92%) of compound **8j**-(*R*) 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_S = 8.61 min, t_R = 7.88 min.

(*S*)-2-(3,3''-Dibromo-[1,1':3',1''-terphenyl]-2'-yl)-2-(picolinamido)ethyl acetate (8j-(*S*)):



The compound **8j**-(*S*) was obtained as a yellow coloured semi-solid (109 mg, 92%, 0.2 mmol scale).

R_f = 0.60 (EtOAc/hexane = 50:50).

IR (DCM): 3375, 1740, 1509 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 8.52 (s, 1H), 8.08 (d, 1H, J = 7.8 Hz), 7.90 (d, 1H, J = 8.5 Hz), 7.80 (t, 1H, J = 7.7 Hz), 7.56-7.17 (m, 12H), 5.71-5.66 (m, 1H), 4.29-4.16 (m, 2H), 1.94 (s, 3H).

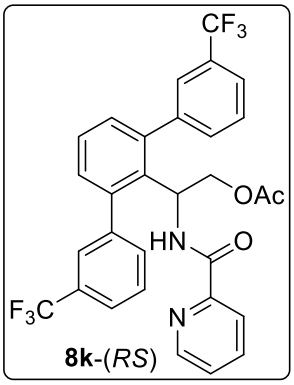
$^{13}C\{^1H\}$ NMR (~101 MHz, $CDCl_3$): δ = 170.7, 163.4, 149.1, 148.3, 143.5, 141.4, 137.1, 133.4, 132.5, 131.0, 130.6, 129.7, 128.2, 127.0, 126.1, 122.5, 122.0, 66.0, 50.3, 20.8.

HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{28}H_{23}Br_2N_2O_3$: 593.0075; found: 593.0046.

$[\alpha]^{25}_D$ = -120.7 (c = 0.06, $CHCl_3$).

The enantiomeric excess (*ee* 92%) of compound **8j**-(*S*) 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_S = 8.42 min, t_R = 7.72 min.

2-(3,3''-Bis(trifluoromethyl)-[1,1':3',1''-terphenyl]-2'-yl)-2-(picolinamido)ethyl acetate (8k-(*RS*)):



The compound **8k**-(*RS*) was obtained as a colourless solid (91 mg, 80%, 0.2 mmol scale).

R_f = 0.50 (EtOAc/hexane = 50:50); mp: 135-137 ^oC.

IR (DCM): 3379, 1745, 1509 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 8.38 (d, 1H, J = 0.24 Hz), 8.06 (d, 1H, J = 7.7 Hz), 7.81-7.37 (m, 12H), 7.22 (d, 2H, J = 7.5 Hz), 5.64-5.59 (m, 1H), 4.26-4.17 (m, 2H), 1.91 (s, 3H).

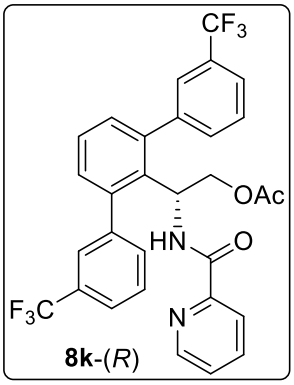
$^{13}C\{^1H\}$ NMR (~101 MHz, $CDCl_3$): δ = 170.5, 163.5, 148.9, 148.0, 142.3, 141.5, 137.1, 133.6, 132.9, 131.3, 130.6 (q, J_{C-F} = 25.9 Hz), 128.8, 127.1, 126.3 (d, J_{C-F} = 2.4 Hz), 126.2, 124.4 (d, J_{C-F} = 2.1 Hz), 124.0 (q, J_{C-F} = 216.7 Hz), 121.9, 65.6, 50.5, 20.6.

$^{19}F\{^1H\}$ NMR (~376 MHz, $CDCl_3$): δ = -62.59.

HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{30}H_{23}F_6N_2O_3$: 573.1613; found: 573.1635.

The HPLC of compound **8k**-(*RS*) was determined by using the Daicel Chiralcel OD-H column, hexane/*i*-PrOH 98:02, flow rate 1.0 mL/min, UV detection at 254 nm, t_S = 9.38 min, t_R = 14.40 min.

(*R*)-2-(3,3''-Bis(trifluoromethyl)-[1,1':3',1''-terphenyl]-2'-yl)-2-(picolinamido)ethyl acetate (8k-(*R*)):



The compound **8k**-(*R*) was obtained as a colourless solid (95 mg, 83%, 0.2 mmol scale).

R_f = 0.60 (EtOAc/hexane = 50:50); mp: 135-137 ^oC.

IR (DCM): 3379, 1745, 1509 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 8.38 (d, 1H, J = 3.4 Hz), 8.06 (d, 1H, J = 7.8 Hz), 7.81-7.68 (m, 10H), 7.40-7.36 (m, 2H), 7.22 (d, 2H, J = 7.6 Hz), 5.63-5.57 (m, 1 H), 4.27-4.16 (m, 2H), 1.91 (s, 3H).

$^{13}C\{^1H\}$ NMR (~101 MHz, $CDCl_3$): δ = 170.6, 163.5, 148.9, 148.0, 142.3, 141.5, 137.1, 133.6, 132.9, 131.3, 130.6 (q, J_{C-F} = 32.1 Hz), 128.8, 127.1, 126.3 (q, J_{C-F} = 3.6 Hz), 126.2, 124.4 (q, J_{C-F} = 3.6 Hz), 124.0 (q, J_{C-F} = 271 Hz), 121.9, 65.8, 50.5, 20.5.

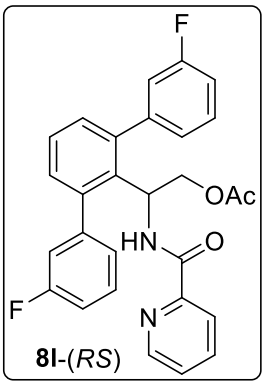
$^{19}F\{^1H\}$ NMR (~376 MHz, $CDCl_3$): δ = -62.59.

HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{30}H_{23}F_6N_2O_3$: 573.1613; found: 573.1639.

$[\alpha]^{25}_D$ = 60.0 (c = 0.08, $CHCl_3$).

The enantiomeric excess (*ee* 91%) of compound **8k**-(*R*) was determined by HPLC using the Daicel Chiralcel OD-H column, hexane/*i*-PrOH 98:02, flow rate 1.0 mL/min, UV detection at 254 nm, t_S = 9.99 min, t_R = 14.28 min.

2-(3,3''-Difluoro-[1,1':3',1''-terphenyl]-2'-yl)-2-(picolinamido)ethyl acetate (8l-(*RS*)):



The compound **8l**-(*RS*) was obtained as a colourless solid (84 mg, 90%, 0.2 mmol scale).

R_f = 0.60 (EtOAc/hexane = 50:50); mp: 128-130 ^oC.

IR (DCM): 3374, 1741, 1509 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 8.46 (d, 1H, J = 3.9 Hz), 8.08 (d, 1H, J = 7.8 Hz), 7.93 (d, 1H, J = 8.7 Hz), 7.80 (t, 1H, J = 7.7 Hz), 7.41-7.11 (m, 12H), 5.76-5.70 (m, 1H), 4.29 (t, 1H, J = 10.6 Hz), 4.17 (dd, 1H, J_1 = 11.3 Hz, J_2 = 4.9 Hz), 1.91 (s, 3H).

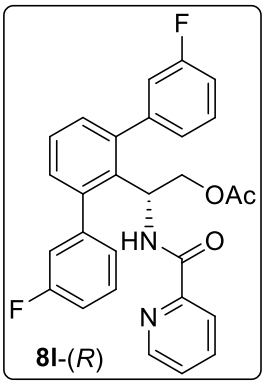
$^{13}C\{^1H\}$ NMR (~101 MHz, $CDCl_3$): δ = 170.7, 163.4, 162.4 (d, J_{C-F} = 245.8 Hz), 149.2, 148.0, 143.5 (d, J_{C-F} = 7.5 Hz), 141.6, 137.1, 133.3, 130.9, 129.8 (d, J_{C-F} = 8.5 Hz), 126.9, 126.1, 125.4 (d, J_{C-F} = 2.4 Hz), 121.9, 116.9 (d, J_{C-F} = 21.4 Hz), 114.5 (d, J_{C-F} = 20.8 Hz), 65.9, 50.3, 20.7.

$^{19}F\{^1H\}$ NMR (~376 MHz, $CDCl_3$): δ = -112.40, -112.96.[18]

HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{28}H_{23}F_2N_2O_3$: 473.1677; found: 473.1661.

The HPLC of compound **8l**-(*RS*) was determined by using the Daicel Chiralpak IC column, hexane/*i*-PrOH 97:03, flow rate 1.0 mL/min, UV detection at 254 nm, t_S = 26.90 min, t_R = 30.67 min.

(*R*)-2-(3,3''-Difluoro-[1,1':3',1''-terphenyl]-2'-yl)-2-(picolinamido)ethyl acetate (8l-(*R*)):



The compound **8l**-(*R*) was obtained as a colourless solid (90 mg, 95%, 0.2 mmol scale).

R_f = 0.60 (EtOAc/hexane = 50:50); mp: 128-130 ºC.

IR (DCM): 3374, 1741, 1579 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 8.46 (d, 1H, J = 4.4 Hz), 8.08 (d, 1H, J = 7.8 Hz), 7.94 (d, 1H, J = 8.8 Hz), 7.80 (t, 1H, J = 7.7 Hz), 7.41-7.11 (m, 12H), 5.76-5.70 (m, 1H), 4.31-4.13 (m, 2H), 1.90 (s, 3H).

$^{13}C\{^1H\}$ NMR (~101 MHz, $CDCl_3$): δ = 170.7, 163.4, 162.4 (d, J_{C-F} = 245.0 Hz), 149.2, 148.0, 143.5 (d, J_{C-F} = 7.6 Hz), 141.6, 137.1, 133.3, 130.9, 129.8 (d, J_{C-F} = 8.5 Hz), 126.9, 126.1, 125.4 (d, J_{C-F} = 2.5 Hz), 121.9, 116.9 (d, J_{C-F} = 21.6 Hz), 114.5 (d, J_{C-F} = 20.8 Hz), 65.9, 50.3, 20.7.

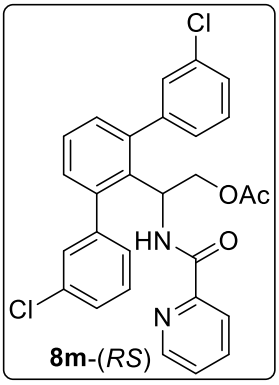
$^{19}F\{^1H\}$ NMR (~376 MHz, $CDCl_3$): δ = -112.46, -113.05.[18]

HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{28}H_{23}F_2N_2O_3$: 473.1677; found: 473.1656.

$[\alpha]^{25}_D$ = 65.2 (*c* = 0.05, $CHCl_3$).

The enantiomeric excess (*ee* >98%) of compound **8l**-(*R*) was determined by HPLC using the Daicel Chiralpak IC column, hexane/*i*-PrOH 97:03, flow rate 1.0 mL/min, UV detection at 254 nm, t_S = not detected min, t_R = 30.26 min.

2-(3,3''-Dichloro-[1,1':3',1''-terphenyl]-2'-yl)-2-(picolinamido)ethyl acetate (8m-(*RS*)):



The compound **8m**-(*RS*) was obtained as a yellow coloured semi-solid (60 mg, 60%, 0.2 mmol scale).

R_f = 0.65 (EtOAc/hexane = 50:50).

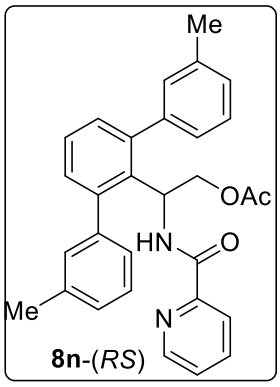
IR (DCM): 3375, 1742, 1511 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 8.50 (s, 1H), 8.08 (d, 1H, J = 7.7 Hz), 7.91 (d, 1H, J = 8.5 Hz), 7.80 (t, 1H, J = 7.6 Hz), 7.40-7.17 (m, 12H), 5.69-5.66 (m, 1H), 4.29-4.16 (m, 2H), 1.93 (s, 3H).

$^{13}C\{^1H\}$ NMR (~101 MHz, $CDCl_3$): δ = 170.7, 163.4, 149.1, 148.3, 143.2, 141.5, 137.1, 134.2, 133.4, 131.0, 129.7, 129.5, 127.7, 127.7, 126.9, 126.1, 122.0, 66.9, 50.3, 20.8.

HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{28}H_{23}Cl_2N_2O_3$: 505.1086; found: 505.1096.

2-(3,3''-Dimethyl-[1,1':3',1''-terphenyl]-2'-yl)-2-(picolinamido)ethyl acetate (8n-(*RS*)):



The compound **8n**-(*RS*) was obtained as a yellow coloured semi-solid (88 mg, 95%, 0.2 mmol scale).

R_f = 0.55 (EtOAc/hexane = 50:50).

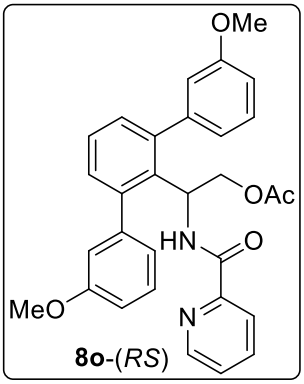
IR (DCM): 3375, 1740, 1508 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 8.46 (d, 1H, J = 4.4 Hz), 8.12 (d, 1H, J = 7.8 Hz), 8.01 (d, 1H, J = 9.1 Hz), 7.77 (t, 1H, J = 7.7 Hz), 7.39-7.20 (m, 12H), 5.90-5.84 (m, 1H), 4.36-4.30 (m, 1H), 4.24 (dd, 1H, J_1 = 11.3 Hz, J_2 = 5.0 Hz), 2.47 (s, 6H) 1.90 (s, 3H).

$^{13}C\{^1H\}$ NMR (~101 MHz, $CDCl_3$): δ = 170.7, 163.3, 149.8, 149.7, 147.8, 143.0, 141.7, 137.8, 137.0, 133.3, 130.6, 130.3, 128.1, 126.6, 126.6, 125.9, 122.1, 66.3, 50.4, 21.5, 20.8.

HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{30}H_{29}N_2O_3$: 465.2178; found: 465.2196.

2-(3,3''-Dimethoxy-[1,1':3',1''-terphenyl]-2'-yl)-2-(picolinamido)ethyl acetate (8o-(*RS*)):



The compound **8o**-(*RS*) was obtained as a yellow coloured semi-solid (83 mg, 84%, 0.2 mmol scale).

R_f = 0.40 (EtOAc/hexane = 50:50).

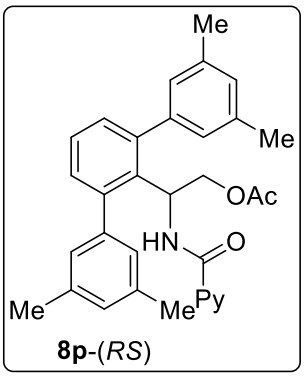
IR (DCM): 3367, 1740, 1510 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 8.43 (d, 1H, J = 4.4 Hz), 8.08 (d, 1H, J = 7.8 Hz), 7.93-7.91 (m, 1H), 7.79 (t, 1H, J = 7.6 Hz), 7.47-6.93 (m, 12H), 5.86-5.80 (m, 1H), 4.40-4.34 (m, 1H), 4.20 (dd, 1H, J_1 = 11.3 Hz, J_2 = 4.8 Hz), 3.95-3.62 (m, 6H), 1.89 (s, 3H).

$^{13}C\{^1H\}$ NMR (~101 MHz, $CDCl_3$): δ = 170.8, 163.5, 159.3, 149.5, 147.9, 142.9, 142.7, 137.0, 133.2, 130.6, 129.3, 126.7, 125.9, 121.9, 121.8, 114.6, 113.6, 66.4, 55.0, 50.3, 20.8.

HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{30}H_{29}N_2O_5$: 497.2076; found: 497.2058.

2-(Picolinamido)-2-(3,3'',5,5''-tetramethyl-[1,1':3',1''-terphenyl]-2'-yl)ethyl acetate (8p-(*RS*)):



The compound **8p**-(*RS*) was obtained as a colourless solid (80 mg, 82%, 0.2 mmol scale).

R_f = 0.60 (EtOAc/hexane = 50:50); mp: 113-115 ^oC.

IR (DCM): 3376, 1742, 1511 cm^{-1}.

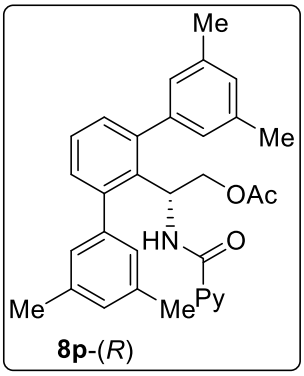
^1H NMR (400 MHz, $CDCl_3$): δ = 8.48 (dd, 1H, J_1 = 4.7 Hz, J_2 = 0.6 Hz), 8.12 (d, 1H, J = 7.8 Hz), 8.02 (d, 1H, J = 9.1 Hz), 7.80 (td, 1H, J_1 = 7.7 Hz, J_2 = 1.7 Hz), 7.41-7.37 (m, 1H), 7.32-7.06 (m, 9H), 5.80-5.78 (m, 1H), 4.26-4.24 (m, 2H), 2.38 (br. s, 12H), 1.92 (s, 3H).

$^{13}C\{^1H\}$ NMR (~101 MHz, $CDCl_3$): δ = 170.7, 163.2, 149.8, 147.9, 143.2, 141.6, 137.6, 137.0, 133.2, 130.4, 129.0, 127.4, 126.5, 125.9, 122.2, 66.4, 50.4, 21.4, 20.9.

HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{32}H_{33}N_2O_3$: 493.2491; found: 493.2501.

The HPLC of compound **8p**-(*RS*) was determined by using the Daicel Chiralpak IC column, hexane/*i*-PrOH 95:05, flow rate 1.0 mL/min, UV detection at 254 nm, t_S = 9.44 min, t_R = 13.80 min.

(*R*)-2-(Picolinamido)-2-(3,3'',5,5''-tetramethyl-[1,1':3',1''-terphenyl]-2'-yl)ethyl acetate (8p-(*R*)):



8p-(*R*)

The compound **8p**-(*R*) was obtained as a colourless solid (90 mg, 92%, 0.2 mmol scale).

R_f = 0.60 (EtOAc/hexane = 50:50); mp: 114-116 °C.

IR (DCM): 3378, 1741, 1510 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 8.43 (d, 1H, *J* = 4.7 Hz), 8.07 (d, 1H, *J* = 7.8 Hz), 7.98 (d, 1H, *J* = 9.1 Hz), 7.75 (td, 1H, J_1 = 7.6 Hz, J_2 = 1.7 Hz), 7.35-7.33 (m, 1 H), 7.26-7.23 (m, 1 H), 7.15-7.01 (m, 6H), 7.01 (s, 2H), 5.76-5.72 (m, 1 H), 4.21-4.19 (m, 2H), 2.32 (br. s, 12H), 1.87 (s, 3H).

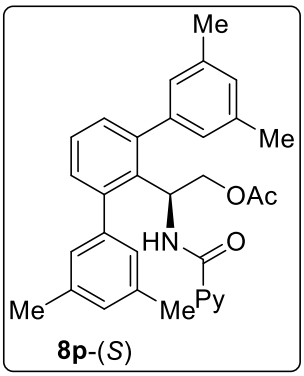
$^{13}C\{^1H\}$ NMR (~126 MHz, $CDCl_3$): δ = 170.6, 163.2, 149.9, 147.9, 143.2, 141.7, 137.6, 137.0, 133.3, 130.4, 129.0, 127.4, 126.5, 125.8, 122.2, 66.4, 50.4, 21.4, 20.8.

HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{32}H_{33}N_2O_3$: 493.2491; found: 493.2511.

$[\alpha]^{25}_D$ = 7.7 (*c* = 0.09, $CHCl_3$).

The enantiomeric excess (*ee* 98%) of compound **8p**-(*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_S = 10.70 min, t_R = 14.66 min.

(*S*)-2-(Picolinamido)-2-(3,3'',5,5''-tetramethyl-[1,1':3',1''-terphenyl]-2'-yl)ethyl acetate (8p-(*S*)):



8p-(*S*)

The compound **8p**-(*S*) was obtained as a colourless solid (92 mg, 95%, 0.2 mmol scale).

R_f = 0.60 (EtOAc/hexane = 50:50); mp: 114-116 °C.

IR (DCM): 3378, 1741, 1510 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 8.49-8.48 (m, 1H), 8.12 (dd, 1H, J_1 = 7.8 Hz, J_2 = 0.9 Hz), 8.03 (d, 1H, *J* = 9.1 Hz), 7.81-7.78 (m, 1H), 7.40-7.37 (m, 1H), 7.32-7.29 (m, 1H), 7.20-7.02 (m, 8H), 5.82-5.77 (m, 1H), 4.26-4.24 (m, 2H), 2.37 (br. s, 12H), 1.92 (s, 3H).

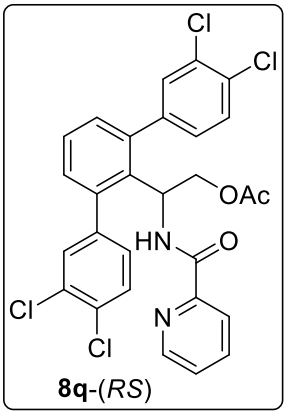
$^{13}C\{^1H\}$ NMR (~126 MHz, $CDCl_3$): δ = 170.6, 163.2, 149.9, 147.9, 143.2, 141.7, 137.6, 137.0, 133.3, 130.4, 129.0, 127.4, 126.5, 125.8, 122.2, 66.4, 50.4, 21.4, 20.8.

HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{32}H_{33}N_2O_3$: 493.2491; found: 493.2511.

$[\alpha]^{25}_{D}$ = -4.7 (*c* = 0.09, $CHCl_3$).

The enantiomeric excess (*ee* 95%) of compound **8p**-(*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_S = 10.43 min, t_R = 15.02 min.

2-(Picolinamido)-2-(3,3'',4,4''-tetrachloro-[1,1':3',1''-terphenyl]-2'-yl)ethyl acetate (8q-(*RS*)):



8q-(*RS*)

The compound **8q**-(*RS*) was obtained as a colourless solid (101 mg, 88%, 0.2 mmol scale).

R_f = 0.70 (EtOAc/hexane = 50:50); mp: 172-174 °C.

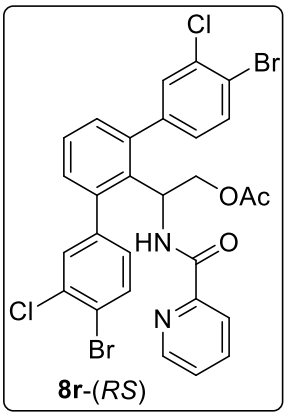
IR (DCM): 3379, 1745, 1513 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.49 (d, 1H, *J* = 4.0 Hz), 8.07 (d, 1H, *J* = 7.8 Hz), 7.87-7.79 (m, 2H), 7.56-7.16 (m, 10H), 5.67-5.62 (m, 1H), 4.28-4.14 (m, 2H), 1.96 (s, 3H).

^{13}C{^{1}H} NMR (~101 MHz, $CDCl_3$): δ = 170.6, 163.4, 148.8, 148.3, 141.4, 140.4, 137.2, 133.4, 132.5, 131.8, 131.4, 131.2, 130.2, 128.8, 127.2, 126.3, 121.9, 65.8, 50.4, 20.8.

HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{28}H_{21}Cl_4N_2O_3$: 573.0306; found: 573.0311.

2-(4,4''-Dibromo-3,3''-difluoro-[1,1':3',1''-terphenyl]-2'-yl)-2-(picolinamido)ethyl acetate (8r-(*RS*)):



8r-(*RS*)

The compound **8r**-(*RS*) was obtained as a colourless solid (94 mg, 75%, 0.2 mmol scale).

R_f = 0.55 (EtOAc/hexane = 50:50); mp: 152-154 °C.

IR (DCM): 3377, 1743, 1514 cm^{-1}.

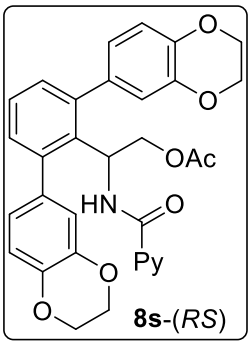
^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.49 (d, 1H, *J* = 4.4 Hz), 8.06 (d, 1H, *J* = 7.8 Hz), 7.86-7.80 (m, 2H), 7.65-7.17 (m, 10H), 5.70-5.64 (m, 1H), 4.26 (t, 1H, *J* = 10.6 Hz), 4.15 (dd, 1H, J_1 = 11.5 Hz, J_2 = 5.0 Hz), 1.94 (s, 3H).

^{13}C{^{1}H} NMR (~101 MHz, $CDCl_3$): δ = 170.6, 163.4, 158.7 (d, $J_{C\text{-}F}$ = 247.5 Hz), 148.8, 148.2, 142.6 (d, $J_{C\text{-}F}$ = 6.9 Hz), 140.6, 137.3, 133.3, 133.2, 131.1, 127.2, 126.4 (d, $J_{C\text{-}F}$ = 2.1 Hz), 126.3, 121.8, 117.9 (d, $J_{C\text{-}F}$ = 22.4 Hz), 108.4 (d, $J_{C\text{-}F}$ = 20.7 Hz), 65.7, 50.4, 20.8.

^{19}F{^{1}H} NMR (~376 MHz, $CDCl_3$): δ = -106.35, -106.92.[18]

HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{28}H_{21}Br_2F_2N_2O_3$: 628.9887; found: 628.9913.

2-(2,6-Bis(2,3-dihydrobenzo[*b*][1,4]dioxin-6-yl)phenyl)-2-(picolinamido)ethyl acetate (8s-(*RS*)):



The compound **8s**-(*RS*) was obtained as a yellow coloured solid (87 mg, 79%, 0.2 mmol scale). R_f = 0.45 (EtOAc/hexane = 50:50); mp: 190-192 ^{o}C.

IR (DCM): 3367, 1740, 1508 cm^{-1}.

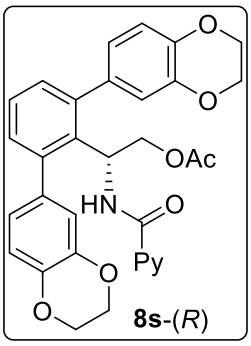
^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.49 (d, 1H, J = 4.4 Hz), 8.11-8.07 (m, 2H), 7.78 (t, 1H, J = 7.6 Hz), 7.40-7.37 (m, 1H), 7.28-7.25 (m, 1H), 7.16 (d, 2H, J = 7.5 Hz), 6.91 (br. s, 6H), 5.87-5.81 (m, 1H), 4.33-4.28 (m, 9H), 4.21-4.17 (m, 1H), 1.93 (s, 3H).

^{13}C{^{1}H} NMR (~101 MHz, $CDCl_3$): δ = 170.7, 163.3, 149.7, 147.8, 143.1, 142.9, 142.3, 137.0, 134.9, 133.8, 130.9, 126.6, 125.8, 122.8, 122.0, 118.6, 116.9, 66.4, 64.4, 50.2, 20.9.

HRMS (ESI): *m/z* [M + H]$^{+}$ calcd for $C_{32}H_{29}N_2O_7$: 553.1975; found: 553.1949.

The HPLC of compound **8s**-(*RS*) was determined by using the Daicel Chiralpak AD column, hexane/*i*-PrOH 90:10, flow rate 1.0 mL/min, UV detection at 254 nm, t_S = 23.78 min, t_R = 21.59 min.

(*R*)-2-(2,6-Bis(2,3-dihydrobenzo[*b*][1,4]dioxin-6-yl)phenyl)-2-(picolinamido)ethyl acetate (8s-(*R*)):



The compound **8s**-(*R*) was obtained as a yellow coloured solid (79 mg, 72%, 0.2 mmol scale).

R_f = 0.45 (EtOAc/hexane = 50:50); mp: 190-192 ^{o}C.

IR (DCM): 3368, 1740, 1508 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.49 (d, 1H, J = 4.3 Hz), 8.11-8.08 (m, 2H), 7.79 (t, 1H, J = 7.6 Hz), 7.40-7.37 (m, 1H), 7.29-7.25 (m, 1H), 7.16 (d, 2H, J = 7.6 Hz), 6.92 (br. s, 6H), 5.87-5.81 (m, 1H), 4.33-4.28 (m, 9H), 4.19 (dd, 1H, J_1 = 11.3 Hz, J_2 = 5.2 Hz), 1.93 (s, 3H).

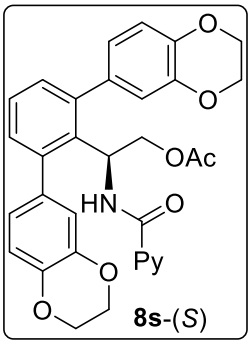
^{13}C{^{1}H} NMR (~101 MHz, $CDCl_3$): δ = 170.7, 163.3, 149.6, 147.8, 143.1, 142.9, 142.3, 137.0, 134.9, 133.7, 130.9, 126.6, 125.9, 122.8, 122.1, 118.6, 116.9, 66.4, 64.4, 50.2, 20.9.

HRMS (ESI): *m/z* [M + H]$^{+}$ calcd for $C_{32}H_{29}N_2O_7$: 553.1975; found: 553.1956.

$[\alpha]^{25}_D$ = 38.1 (c = 0.04, $CHCl_3$).

The enantiomeric excess (*ee* 98%) of compound **8s**-(*R*) was determined by HPLC using the Daicel Chiralpak AD column, hexane/*i*-PrOH 90:10, flow rate 1.0 mL/min, UV detection at 254 nm, t_S = 23.93 min, t_R = 21.43 min.

(*S*)-2-(2,6-Bis(2,3-dihydrobenzo[*b*][1,4]dioxin-6-yl)phenyl)-2-(picolinamido)ethyl acetate (8s-(*S*)):



The compound **8s**-(*S*) was obtained as a yellow coloured solid (88 mg, 80%, 0.2 mmol scale).

R_f = 0.45 (EtOAc/hexane = 50:50); mp: 190-192 ^oC.

IR (DCM): 3367, 1739, 1508 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 8.49 (d, 1H, J = 4.4 Hz), 8.11-8.07 (m, 2H), 7.78 (t, 1H, J = 7.7 Hz), 7.40-7.36 (m, 1H), 7.28-7.25 (m, 1H), 7.16 (d, 2H, J = 7.5 Hz), 6.91 (br. s, 6H), 5.87-5.81 (m, 1H), 4.33-4.28 (m, 9H), 4.22-4.17 (m, 1H), 1.93 (s, 3H).

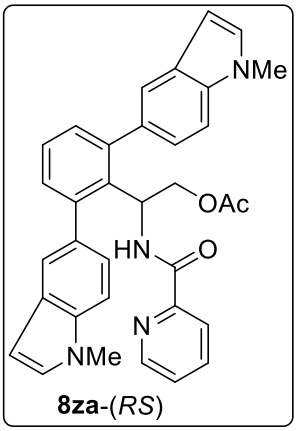
$^{13}C\{^1H\}$ NMR (~101 MHz, $CDCl_3$): δ = 170.7, 163.3, 149.6, 147.8, 143.1, 142.9, 142.3, 137.0, 134.9, 133.7, 130.9, 126.6, 125.8, 122.8, 122.1, 118.6, 116.9, 66.4, 64.4, 50.2, 20.9.

HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{32}H_{29}N_2O_7$: 553.1975; found: 553.1957.

$[\alpha]^{25}_D$ = -27.6 (c = 0.04, $CHCl_3$).

The enantiomeric excess (*ee* 98%) of compound **8s**-(*S*) was determined by HPLC using the Daicel Chiralpak AD column, hexane/*i*-PrOH 90:10, flow rate 1.0 mL/min, UV detection at 254 nm, t_S = 23.69 min, t_R = 21.96 min.

2-(2,6-Bis(1-methyl-1*H*-indol-5-yl)phenyl)-2-(picolinamido)ethyl acetate (8za-(*RS*)):



The compound **8za**-(*RS*) was obtained as a red coloured semi-solid (46 mg, 42%, 0.20 mmol scale).

R_f = 0.35 (EtOAc/hexane = 50:50).

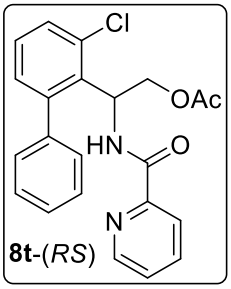
IR (DCM): 3369, 1740, 1510 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 8.17 (br. s, 1H), 8.02 (d, 1H, J = 7.8 Hz), 7.72-7.09 (m, 14H), 6.46 (br. s, 2H), 5.93-5.87 (m, 1H), 4.26-4.18 (m, 2H), 3.83 (s, 6H), 1.79 (s, 3H).

$^{13}C\{^1H\}$ NMR (~101 MHz, $CDCl_3$): δ = 170.7, 163.1, 149.8, 147.5, 143.9, 136.7, 135.9, 134.1, 132.9, 131.0, 129.3, 128.2, 126.1, 125.5, 123.5, 121.9, 121.8, 108.7, 101.1, 66.7, 50.2, 32.9, 20.8.

HRMS (ESI): *m/z* $[M+H]^+$ calcd for $C_{34}H_{31}N_4O_3$: 543.2396; found: 543.2398.

2-(3-Chloro-[1,1'-biphenyl]-2-yl)-2-(picolinamido)ethyl acetate (8t-(*RS*)):



The compound **8t**-(*RS*) was obtained as a yellow coloured semi-solid (31 mg, 43%, 0.18 mmol scale).

R_f = 0.60 (EtOAc/hexane = 50:50).

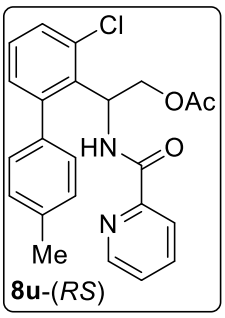
IR (DCM): 3382, 1743, 1510 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.09 (br. s, 1H), 8.58 (d, 1H, J = 4.3 Hz), 8.14 (d, 1H, J = 7.8 Hz), 7.82 (t, 1H, J = 7.6 Hz), 7.51-7.16 (m, 9H), 5.89-5.83 (m, 1H), 4.71-4.65 (m, 1H), 4.44 (dd, 1H, J_1 = 11.2 Hz, J_2 = 5.8 Hz), 1.96 (s, 3H).

^{13}C{^{1}H} NMR (~101 MHz, $CDCl_3$): δ = 170.7, 163.6, 149.6, 148.2, 145.4, 140.2, 137.2, 133.9, 132.9, 130.2, 129.7, 129.4, 128.6, 128.3, 127.9, 126.2, 122.2, 64.2, 49.7, 20.8.

HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{22}H_{20}ClN_2O_3$: 395.1162; found: 395.1172.

2-(3-Chloro-4'-methyl-[1,1'-biphenyl]-2-yl)-2-(picolinamido)ethyl acetate (8u-(*RS*)):



The compound **8u**-(*RS*) was obtained as a yellow coloured semi-solid (46 mg, 51%, 0.22 mmol scale).

R_f = 0.65 (EtOAc/hexane = 50:50).

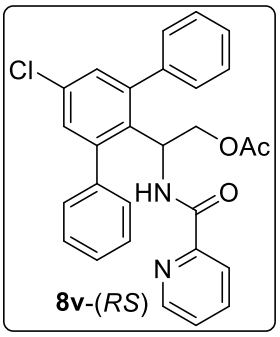
IR (DCM): 3375, 1751, 1507 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.10 (br. s, 1H), 8.58 (d, 1H, J = 4.5 Hz), 8.14 (d, 1H, J = 7.8 Hz), 7.82 (t, 1H, J = 7.7 Hz), 7.44-7.15 (m, 8H), 5.91-5.85 (m, 1H), 4.66 (t, 1H, J = 10.7 Hz), 4.44 (dd, 1H, J_1 = 11.2 Hz, J_2 = 5.8 Hz), 2.45 (s, 3H), 1.97 (s, 3H).

^{13}C{^{1}H} NMR (~101 MHz, $CDCl_3$): δ = 170.8, 163.6, 149.7, 148.2, 145.4, 137.5, 137.3, 137.2, 133.9, 132.9, 130.1, 129.8, 129.2, 129.0, 128.5, 126.1, 122.2, 64.2, 49.7, 21.3, 20.8.

HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{23}H_{22}ClN_2O_3$: 409.1319; found: 409.1337.

2-(5'-Chloro-[1,1':3',1''-terphenyl]-2'-yl)-2-(picolinamido)ethyl acetate (8v-*RS*)):



The compound **8v**-(*RS*) was obtained as a yellow coloured semi-solid (76 mg, 90%, 0.18 mmol scale).

R_f = 0.65 (EtOAc/hexane = 50:50).

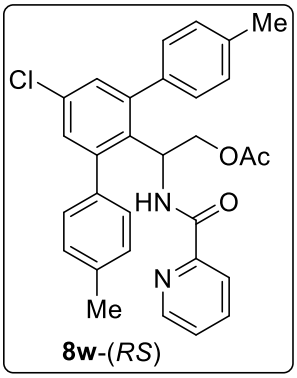
IR (DCM): 3372, 1741, 1507 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.42 (d, 1H, J = 4.3 Hz), 8.08 (d, 1H, J = 7.8 Hz), 7.88-7.77 (m, 2H), 7.44-7.27 (m, 11H), 7.22 (s, 2H), 5.72-5.66 (m, 1H), 4.25 (t, 1H, J = 10.5 Hz), 4.15 (dd, 1H, J_1 = 11.4 Hz, J_2 = 4.9 Hz), 1.88 (s, 3H).

^{13}C{^{1}H} NMR (~101 MHz, $CDCl_3$): δ = 170.6, 163.4, 149.3, 147.8, 144.6, 140.4, 137.1, 132.2, 132.2, 130.5, 129.4, 128.3, 127.8, 126.0, 122.0, 65.8, 50.0, 20.7.

HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{28}H_{24}ClN_2O_3$: 471.1475; found: 471.1463.

2-(5'-Chloro-4,4''-dimethyl-[1,1':3',1''-terphenyl]-2'-yl)-2-(picolinamido)ethyl acetate (8w-(*RS*)):



The compound **8w**-(*RS*) was obtained as a yellow coloured semi-solid (87 mg, 80%, 0.22 mmol scale).

R_f = 0.65 (EtOAc/hexane = 50:50).

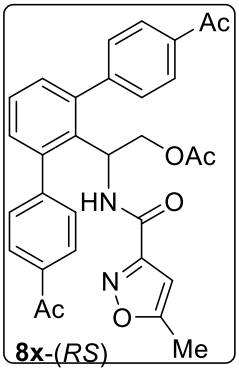
IR (DCM): 3372, 1741, 1509 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 8.44 (d, 1H, J = 4.4 Hz), 8.08 (d, 1H, J = 7.8 Hz), 7.90 (d, 1H, J = 8.9 Hz), 7.80 (t, 1H, J = 7.6 Hz), 7.46-7.02 (m, 11H), 5.75-5.72 (m, 1H), 4.23 (t, 1H, J = 10.6 Hz), 4.15 (dd, 1H, J_1 = 11.4 Hz, J_2 = 5.2 Hz), 2.45 (s, 6H), 1.90 (s, 3H).

$^{13}C\{^1H\}$ NMR (~101 MHz, $CDCl_3$): δ = 170.7, 163.3, 149.4, 147.7, 144.6, 137.5, 137.5, 137.1, 132.4, 132.1, 130.5, 129.2, 129.0, 126.0, 122.0, 66.0, 49.9, 20.3, 20.8.

HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{30}H_{28}ClN_2O_3$: 499.1788; found: 499.1773.

2-(4,4''-Diacetyl-[1,1':3',1''-terphenyl]-2'-yl)-2-(5-methylisoxazole-3-carboxamido)ethyl acetate (8x-(*RS*)):



The compound **8x**-(*RS*) was obtained as a yellow coloured semi-solid (70 mg, 67%, 0.2 mmol scale).

R_f = 0.30 (EtOAc/hexane = 50:50).

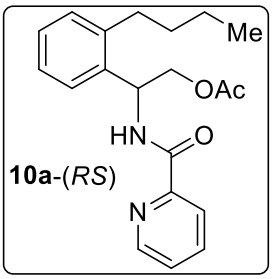
IR (DCM): 3401, 1740, 1599 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 8.04 (br. s, 4H), 7.53-7.36 (m, 5H), 7.19 (d, 2H, J = 7.6 Hz), 6.52 (d, 1H, J = 8.1 Hz), 6.30 (s, 1H), 5.58-5.52 (m, 1H), 4.17 (dd, 1H, J = 11.2 Hz), 4.08 (dd, 1H, J_1 = 11.6 Hz, J_2 = 4.8 Hz), 2.67 (s, 6H), 2.45 (s, 3H), 1.89 (s, 3H).

$^{13}C\{^1H\}$ NMR (~101 MHz, $CDCl_3$): δ = 197.7, 171.2, 170.6, 158.3, 157.9, 146.2, 141.8, 136.3, 132.3, 130.8, 129.7, 128.4, 127.3, 101.0, 65.3, 50.8, 26.7, 20.7, 12.3.

HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{31}H_{29}N_2O_6$: 525.2026; found: 525.2007.

2-(2-Butylphenyl)-2-(picolinamido)ethyl acetate (10a-(*RS*)):



The Compound **10a**-(*RS*) was obtained as a colourless semi-solid (28 mg, 42%, 0.2 mmol scale).

R_f = 0.65 (EtOAc/hexane = 50:50).

IR (DCM): 3375, 1738, 1220 cm^{-1}.

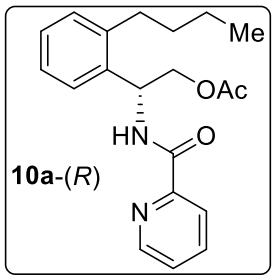
^1H NMR (400 MHz, $CDCl_3$): δ = 8.60-8.57 (m, 2H), 8.19 (d, 1H, J = 7.8 Hz), 7.89-7.84 (m, 1H), 7.47-7.39 (m, 2H), 7.26-7.23 (m, 3H), 5.78-5.73 (m, 1H), 4.45-4.42 (m, 2H), 2.85-2.80 (m, 2H), 2.07 (s, 3H), 1.72-1.63 (m, 2H), 1.49-1.44 (m, 2H), 0.97 (t, 3H, J = 7.3 Hz).

$^{13}C\{^{1}H\}$ NMR (~101 MHz, $CDCl_3$): δ = 171.0, 163.8, 149.6, 148.2, 141.1, 137.4, 136.1, 130.0, 128.0, 126.3, 126.0, 125.8, 122.4, 66.1, 48.4, 33.6, 32.5, 22.8, 20.9, 14.0.

HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{20}H_{25}N_2O_3$: 341.1865; found: 341.1878.

The HPLC of compound **10a**-(*RS*) was determined by using the Daicel Chiralpak IA column, hexane/*i*-PrOH 90:10, flow rate 1.0 mL/min, UV detection at 254 nm, t_S = 5.67 min, t_R = 9.29 min.

(*R*)-2-(2-Butylphenyl)-2-(picolinamido)ethyl acetate (10a-(*R*)):



The compound **10a**-(*R*) was obtained as a colourless semi-solid (30 mg, 45%, 0.2 mmol scale).

R_f = 0.65 (EtOAc/hexane = 50:50).

IR (DCM): 3377, 1738, 1225 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.57-8.56 (m, 2H), 8.18-8.16 (m, 1H), 7.83 (td, 1H, J_1 = 7.7 Hz, J_2 = 1.6 Hz), 7.43-7.38 (m, 2H), 7.23-7.20 (m, 3H), 5.78-5.74 (m, 1H), 4.45-4.39 (m, 2H), 2.83-2.78 (m, 2H), 2.04 (s, 3H), 1.70-1.63 (m, 2H), 1.47-1.42 (m, 2H), 0.95 (t, 3H, *J* = 7.4 Hz).

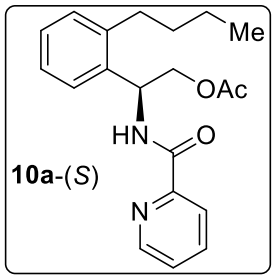
$^{13}C\{^{1}H\}$ NMR (~126 MHz, $CDCl_3$): δ = 171.0, 163.8, 149.6, 148.2, 141.1, 137.4, 136.1, 130.0, 127.9, 126.3, 126.3, 126.0, 122.3, 66.1, 48.4, 33.6, 32.5, 22.8, 20.9, 14.0.

HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{20}H_{25}N_2O_3$: 341.1865; found: 341.1855.

$[\alpha]^{25}_D$ = 14.7 (*c* = 0.08, $CHCl_3$).

The enantiomeric excess (*ee* 97%) of compound **10a**-(*R*) was determined by HPLC using the Daicel Chiralpak IA column, hexane/*i*-PrOH 90:10, flow rate 1.0 mL/min, UV detection at 254 nm, t_S = 6.70 min, t_R = 10.78 min.

(*S*)-2-(2-Butylphenyl)-2-(picolinamido)ethyl acetate (10a-(*S*)):



The compound **10a**-(*S*) was obtained as a colourless semi-solid (30 mg, 46%, 0.2 mmol scale).

R_f = 0.65 (EtOAc/hexane = 50:50).

IR (DCM): 3377, 1740 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.60-8.58 (m, 2H), 8.19 (d, 1H, *J* = 7.8 Hz), 7.86 (t, 1H, *J* = 7.7 Hz) 7.46-7.40 (m, 2H), 7.30-7.24 (m, 3H), 5.81-5.75 (m, 1H), 4.48-4.41 (m, 2H), 2.85-2.80 (m, 2H), 2.06 (s, 3H), 1.74-1.63 (m, 2H), 1.51-1.42 (m, 2H), 0.97 (t, 3H, *J* = 7.3 Hz).

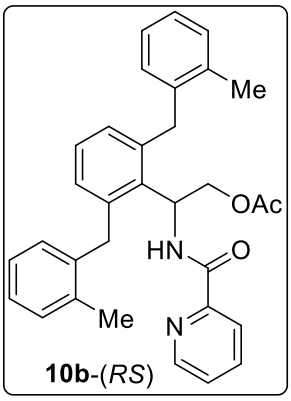
$^{13}C\{^{1}H\}$ NMR (~101 MHz, $CDCl_3$): δ = 171.0, 163.8, 149.6, 148.2, 141.1, 137.4, 136.1, 130.0, 128.0, 126.3, 126.0, 125.8, 122.4, 66.1, 48.4, 33.6, 32.5, 22.8, 20.9, 14.0.

HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{20}H_{25}N_2O_3$: 341.1865; found: 341.1880.

$[\alpha]^{25}_D$ = -8.8 (*c* = 0.08, $CHCl_3$).

The enantiomeric excess (*ee* 98%) of compound **10a**-(*S*) was determined by HPLC using the Daicel Chiralpak IA column, hexane/*i*-PrOH 90:10, flow rate 1.0 mL/min, UV detection at 254 nm, t_S = 6.53 min, t_R = 10.42 min.

2-(2,6-Bis(2-methylbenzyl)phenyl)-2-(picolinamido)ethyl acetate (10b-(*RS*)):



The compound **10b**-(*RS*) was obtained (from procedure D) as a colourless solid (69 mg, 71%, 0.2 mmol scale).

R_f = 0.60 (EtOAc/hexane = 50:50); mp: 142-144 ºC.

IR (DCM): 3380 1739, 1509 cm^{-1}.

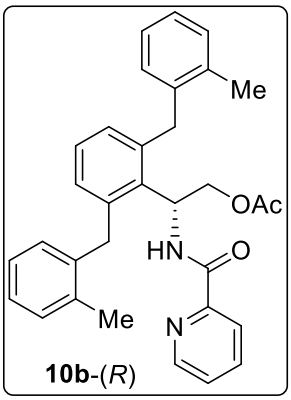
^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.62 (d, 1H, *J* = 7.7 Hz), 8.35 (d, 1H, *J* = 4.6 Hz), 8.02 (d, 1H, *J* = 7.8 Hz), 7.75 (t, 1H, *J* = 7.7 Hz), 7.35-7.32 (m, 1H), 7.17-6.91 (m, 11H), 5.91-5.58 (m, 1H), 4.74 (t, 1H, *J* = 10.8 Hz), 4.48 (br. s, 2H), 4.24-4.15 (m, 2H), 3.94 (dd, 1H, J_1 = 11.7 Hz, J_2 = 4.4 Hz), 2.39 (s, 6H), 2.00 (s, 3H).

^{13}C{^{1}H} NMR (~101 MHz, $CDCl_3$): δ = 171.3, 164.1, 149.3, 147.9, 138.7, 136.9, 136.5, 134.8, 130.0, 129.4, 129.4, 129.3, 128.0, 126.2, 126.0, 125.8, 121.8, 64.7, 49.8, 37.6, 20.8, 19.9.

HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{32}H_{33}N_2O_3$: 493.2491; found: 493.2477.

The HPLC of compound **10b**-(*RS*) was determined by using the Daicel Chiralpak ADH column, hexane/*i*-PrOH 90:10, flow rate 1.0 mL/min, UV detection at 254 nm, t_S = 8.28 min, t_R = 11.37 min.

(*R*)-2-(2,6-Bis(2-methylbenzyl)phenyl)-2-(picolinamido)ethyl acetate (10b-(*R*)):



The compound **10b**-(*R*) was obtained (from procedure D) as a colourless solid (45 mg, 46%, 0.2 mmol scale).

R_f = 0.60 (EtOAc/hexane = 50:50); mp: 142-144 ºC.

IR (DCM): 3380, 1739, 1450 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.62 (d, 1H, *J* = 7.7 Hz), 8.35 (d, 1H, *J* = 4.6 Hz), 8.02 (d, 1H, *J* = 7.8 Hz), 7.75 (t, 1H, *J* = 7.7 Hz), 7.35-6.90 (m, 12H), 5.90-5.58 (m, 1H), 4.74 (t, 1H, *J* = 10.8 Hz), 4.51-4.45 (m, 2H), 4.21 (d, 1H, *J* = 16.2 Hz), 3.94 (dd, 1H, J_1 = 11.7 Hz, J_2 = 4.4 Hz), 2.38 (s, 6H), 2.00 (s, 3H).

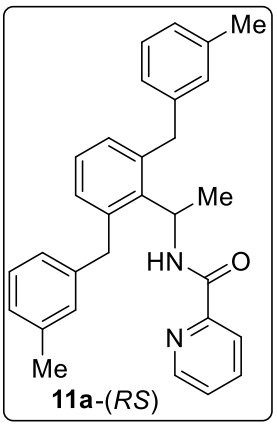
^{13}C{^{1}H} NMR (~101 MHz, $CDCl_3$): δ = 171.3, 164.1, 149.3, 147.9, 138.7, 136.9, 136.4, 134.8, 130.0, 129.4, 129.4, 129.4, 128.0, 126.2, 126.0, 125.8, 121.8, 64.7, 49.8, 37.6, 20.8, 19.8.

HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{32}H_{33}N_2O_3$: 493.2491; found: 493.2509.

$[\alpha]^{25}_D$ = 95.6 (*c* = 0.05, $CHCl_3$).

The enantiomeric excess (*ee* 94%) of compound **10b**-(*R*) was determined by HPLC using the Daicel Chiralpak ADH column, hexane/*i*-PrOH 90:10, flow rate 1.0 mL/min, UV detection at 254 nm, t_S = 8.39 min, t_R = 11.67 min.

***N*-(1-(2,6-Bis(3-methylbenzyl)phenyl)ethyl)picolinamide (11a-(*RS*)):**



The compound **11a**-(*RS*) was obtained (from procedure D) as a colourless semi-solid (47 mg, 55%, 0.20 mmol scale).

R_f = 0.6 (EtOAc/hexane = 20:80).

IR (DCM): 3392, 1673, 1508 cm^{-1}.

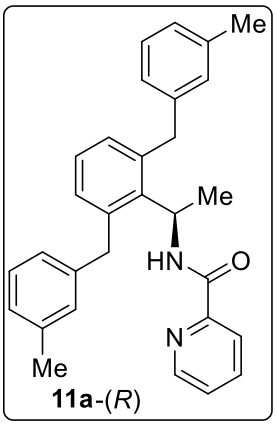
^1H NMR (400 MHz, $CDCl_3$): δ = 8.33 (d, 1H, J = 7.2 Hz), 8.28 (d, 1H, J = 4.7 Hz), 8.03 (d, 1H, J = 7.8 Hz), 7.72 (td, 1H, J_1 = 7.7 Hz, J_2 = 1.7 Hz), 7.30-7.27 (m, 1H), 7.16-6.88 (m, 11H), 5.72-5.65 (m, 1H), 4.41 (br. s, 2H), 4.17 (d, 2H, J = 16.0 Hz), 2.20 (s, 6H), 1.24 (d, 3H, J = 7.2 Hz).

$^{13}C\{^1H\}$ NMR (~101 MHz, $CDCl_3$): δ = 163.4, 149.6, 147.7, 141.0, 139.7, 138.8, 137.7, 136.9, 130.4, 129.5, 128.1, 127.1, 126.5, 125.9, 125.6, 121.7, 45.5, 39.8, 21.3, 20.4.

HRMS (ESI): *m/z* $[M+H]^+$ calcd for $C_{30}H_{31}N_2O$: 435.2436; found: 435.2434.

The HPLC of compound **11a**-(*RS*) was determined by using the Daicel Chiralcel OD-H column, hexane/*i*-PrOH 90:10, flow rate 1.0 mL/min, UV detection at 254 nm, t_R = 7.84 min, t_S = 10.68 min.

(*R*)-*N*-(1-(2,6-Bis(3-methylbenzyl)phenyl)ethyl)picolinamide (11a-(*R*)):



The compound **11a**-(*R*) was obtained (from procedure D) as a colourless semi-solid (40 mg, 47%, 0.20 mmol scale).

R_f = 0.6 (EtOAc/hexane = 20:80).

IR (DCM): 391, 1673, 1510 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 8.33 (d, 1H, J = 7.2 Hz), 8.28 (d, 1H, J = 4.7 Hz), 8.03 (d, 1H, J = 7.8 Hz), 7.72 (td, 1H, J_1 = 7.7 Hz, J_2 = 1.7 Hz), 7.30-7.27 (m, 1H), 7.16-6.88 (m, 11H), 5.72-5.65 (m, 1H), 4.41 (br. s, 2H), 4.17 (d, 2H, J = 16.0 Hz), 2.20 (s, 6H), 1.24 (d, 3H, J = 7.2 Hz).

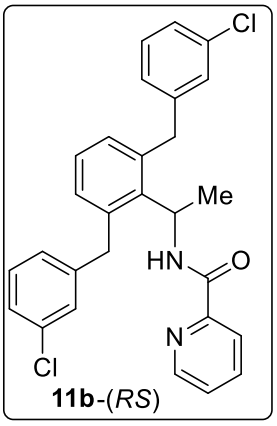
$^{13}C\{^1H\}$ NMR (~101 MHz, $CDCl_3$): δ = 163.4, 149.6, 147.7, 141.0, 139.7, 138.7, 137.7, 136.9, 130.4, 129.5, 128.1, 127.1, 126.5, 125.9, 125.6, 121.7, 45.5, 39.8, 21.3, 20.4.

HRMS (ESI): *m/z* $[M+H]^+$ calcd for $C_{30}H_{31}N_2O$: 435.2436; found: 435.2435.

$[\alpha]^{25}_D$ = -65.1 (c = 0.04, $CHCl_3$).

The enantiomeric excess (*ee* 92%) of compound **11a**-(*R*) was determined by HPLC using the Daicel Chiralcel OD-H column, hexane/*i*-PrOH 90:10, flow rate 1.0 mL/min, UV detection at 254 nm, t_R = 7.82 min, t_S = 10.75 min.

***N*-(1-(2,6-Bis(3-chlorobenzyl)phenyl)ethyl)picolinamide (11b-*(RS)*):**



11b-(*RS*)

The compound **11b**-(*RS*) was obtained (from procedure D) as a colourless semi-solid (53 mg, 56%, 0.20 mmol scale).

R_f = 0.65 (EtOAc/hexane = 20:80).

IR (DCM): 3389, 1673, 1510 cm^{-1}.

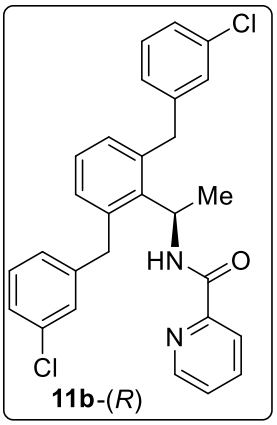
^1H NMR (400 MHz, $CDCl_3$): δ = 8.29 (d, 1H, J = 4.6 Hz), 8.22 (d, 1H, J = 7.0 Hz), 7.99 (d, 1H, J = 7.8 Hz), 7.71 (td, 1H, J_1 = 7.7 Hz, J_2 = 1.6 Hz), 7.31-7.28 (m, 1H), 7.23-7.00 (m, 11H), 5.59-5.52 (m, 11H), 4.46 (br. s, 2H), 4.16 (d, 2H, J = 16.2 Hz), 1.23 (d, 3H, J = 7.2 Hz).

$^{13}C\{^1H\}$ NMR (~101 MHz, $CDCl_3$): δ = 163.5, 149.2, 147.7, 143.1, 139.9, 137.8, 136.9, 134.0, 130.9, 129.4, 128.7, 127.4, 126.8, 125.9, 125.7, 121.7, 45.5, 39.5, 20.4.

HRMS (ESI): *m/z* $[M+H]^+$ calcd for $C_{28}H_{25}Cl_2N_2O$: 475.1344; found: 475.1342.

The HPLC of compound **11b**-(*RS*) was determined by using the Daicel Chiralcel OD-H column, hexane/i-PrOH 90:10, flow rate 1.0 mL/min, UV detection at 254 nm, t_R = 9.82 min, t_S = 12.23 min.

(*R*)-*N*-(1-(2,6-Bis(3-chlorobenzyl)phenyl)ethyl)picolinamide (11b-(*R*)):



11b-(*R*)

The compound **11b**-(*R*) was obtained as a colourless semi-solid (55 mg, 58%, 0.20 mmol scale).

R_f = 0.65 (EtOAc/hexane = 20:80).

IR (DCM): 3388, 1672, 1508 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 8.28 (d, 1H, J = 4.6 Hz), 8.22 (d, 1H, J = 7.0 Hz), 7.99 (d, 1H, J = 7.8 Hz), 7.71 (td, 1H, J_1 = 7.7 Hz, J_2 = 1.6 Hz), 7.32-7.00(m, 11H), 5.59-5.52 (m, 1H), 4.46 (br. s, 2H), 4.16 (d, 2H, J = 16.2 Hz), 1.23 (d, 3H, J = 7.2 Hz).

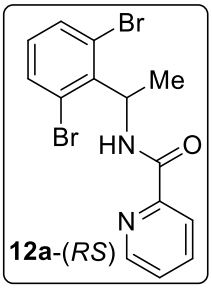
$^{13}C\{^1H\}$ NMR (~101 MHz, $CDCl_3$): δ = 163.6, 149.3, 147.8, 143.2, 140.0, 137.9, 137.0, 134.1, 131.0, 129.5, 128.8, 127.5, 126.9, 126.0, 125.8, 121.8, 45.6, 39.6, 20.5.

HRMS (ESI): *m/z* $[M+H]^+$ calcd for $C_{28}H_{25}Cl_2N_2O$: 475.1344; found: 475.1342.

$[\alpha]^{25}_D$ = -47.1 (c = 0.04, $CHCl_3$).

The enantiomeric excess (*ee* 98%) of compound **11b**-(*R*) was determined by HPLC using the Daicel Chiralcel OD-H column, hexane/i-PrOH 90:10, flow rate 1.0 mL/min, UV detection at 254 nm, t_R = 9.74 min, t_S = 11.98 min.

***N*-(1-(2,6-Dibromophenyl)ethyl)picolinamide (12a-(*RS*)):**



The compound **12a**-(*RS*) was obtained as a colourless solid (55 mg, 57%, 0.25 mmol scale).

R_f = 0.55 (EtOAc/hexane = 20:80); mp: 100-102 ºC.

IR (DCM): 3391, 1676, 1506 cm^{-1}.

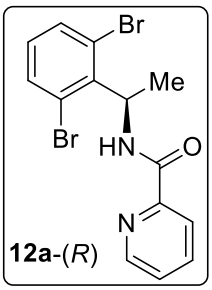
^1H NMR (400 MHz, $CDCl_3$): δ = 9.19 (d, 1H, J = 7.9 Hz), 8.58 (d, 1H, J = 4.5 Hz), 8.16 (d, 1H, J = 7.7 Hz), 7.81 (t, 1H, J = 7.6 Hz), 7.55-7.45 (m, 2H), 7.43-7.40 (m, 1H), 6.93 (t, 1H, J = 8.0 Hz), 6.20-6.12 (m, 1H), 1.70 (d, 3H, J = 7.2 Hz).

$^{13}C\{^1H\}$ NMR (~126 MHz, $CDCl_3$): δ = 163.1, 149.6, 148.1, 139.5, 137.2, 133.9, 132.8, 129.3, 126.1, 122.3, 50.1, 18.4.

HRMS (ESI): *m/z* $[M+H]^+$ calcd for $C_{14}H_{13}Br_2N_2O$: 382.9395; found: 382.9386.

The HPLC of compound **12a**-(*RS*) was determined by using the Daicel Chiralpak IC column, hexane/*i*-PrOH 80:20, flow rate 1.0 mL/min, UV detection at 254 nm, t_S = 14.11 min, t_R = 15.93 min.

(*R*)-*N*-(1-(2,6-Dibromophenyl)ethyl)picolinamide (12a-(*R*)):



The compound **12a**-(*R*) was obtained as a colourless solid (54 mg, 56%, 0.25 mmol scale).

R_f = 0.55 (EtOAc/hexane = 20:80); mp: 101-103 ºC.

IR (DCM): 3390, 1676, 1506 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 9.19 (d, 1H, J = 8.1 Hz), 8.59 (dd, 1H, J_1 = 4.7 Hz, J_2 = 0.7 Hz), 8.16 (d, 1H, J = 7.8 Hz), 7.82 (td, 1H, J_1 = 7.7 Hz, J_2 = 1.7 Hz), 7.55-7.45 (m, 2H), 7.44-7.40 (m, 1H), 6.93 (t, 1H, J = 8.0 Hz), 6.20-6.12 (m, 1H), 1.71 (d, 3H, J = 7.2 Hz).

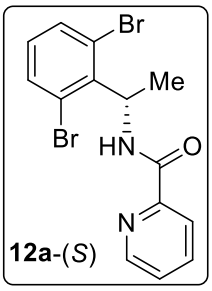
$^{13}C\{^1H\}$ NMR (~126 MHz, $CDCl_3$): δ = 163.2, 149.8, 148.2, 139.7, 137.3. 134.0, 132.9, 129.4, 126.1, 122.4, 50.2, 18.5.

HRMS (ESI): *m/z* $[M+H]^+$ calcd for $C_{14}H_{13}Br_2N_2O$: 382.9395; found: 382.9402.

$[\alpha]^{25}_D$ = -148.0 (c = 0.07, $CHCl_3$).

The enantiomeric excess (*ee* 94%) of compound **12a**-(*R*) was determined by HPLC using the Daicel Chiralpak IC column, hexane/*i*-PrOH 80:20, flow rate 1.0 mL/min, UV detection at 254 nm, t_S = 14.11 min, t_R = 15.93 min.

(*S*)-*N*-(1-(2,6-Dibromophenyl)ethyl)picolinamide (12a-(*S*)):



The compound **12a**-(*S*) was obtained as a colourless solid (55 mg, 57%, 0.25 mmol scale).

R_f = 0.55 (EtOAc/hexane = 20:80); mp: 101-103 °C.

IR (DCM): 3385, 1676, 1507 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 9.19 (d, 1H, J = 8.2 Hz), 8.60-8.58 (m, 1H), 8.16 (d, 1H, J = 7.8 Hz), 7.82 (td, 1H, J_1 = 7.7 Hz, J_2 = 1.7 Hz), 7.55-7.45 (m, 2H), 7.43-7.40 (m, 1H), 6.93 (t, 1H, J = 8.0 Hz), 6.20-6.12 (m, 1H), 1.70 (d, 3H, J = 7.2 Hz).

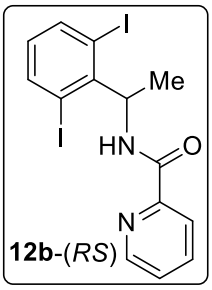
$^{13}C\{^1H\}$ NMR (~126 MHz, $CDCl_3$): δ = 163.2, 149.7, 148.2, 139.7, 137.4, 134.0, 133.0, 129.4, 126.1, 122.4, 50.2, 18.5.

HRMS (ESI): *m/z* $[M+H]^+$ calcd for $C_{14}H_{13}Br_2N_2O$: 382.9395; found: 382.9403.

$[\alpha]^{25}_D$ = +137.2 (c = 0.07, $CHCl_3$).

The enantiomeric excess (*ee* 99%) of compound **12a**-(*S*) was determined by HPLC using the Daicel Chiralpak IC column, hexane/*i*-PrOH 80:20, flow rate 1.0 mL/min, UV detection at 254 nm, t_S = 14.05 min, t_R = 15.97 min.

***N*-(1-(2,6-Diiodophenyl)ethyl)picolinamide (12b-(*RS*)):**



The compound **12b**-(*RS*) was obtained as a colourless solid (105 mg, 88%, 0.25 mmol scale).

R_f = 0.6 (EtOAc/hexane = 20:80); mp: 112-114 °C.

IR (DCM): 3383, 1671, 1507 cm^{-1}.

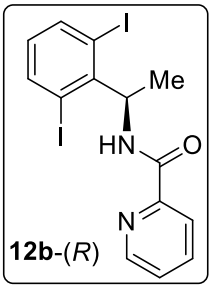
^1H NMR (400 MHz, $CDCl_3$): δ = 9.19 (d, 1H, J = 7.2 Hz), 8.60 (d, 1H, J = 4.4 Hz), 8.15 (d, 1H, J = 7.8 Hz), 7.89-7.79 (m, 3H), 7.44-7.41 (m, 1H), 6.54 (t, 1H, J = 7.8 Hz), 5.86-5.79 (m, 1H), 1.66 (d, 3H, J = 7.3 Hz).

^{13}C NMR (~101 MHz, $CDCl_3$): δ = 162.9, 149.5, 148.1, 143.1, 142.3, 140.4, 137.2, 130.1, 126.1, 122.2, 57.2, 18.1.

HRMS (ESI): *m/z* $[M+H]^+$ calcd for $C_{14}H_{13}I_2N_2O$: 478.9117; found: 478.9106.

The HPLC of compound **12b**-(*RS*) was determined by using the Daicel Chiralcel OD-H column, hexane/*i*-PrOH 90:10, flow rate 1.0 mL/min, UV detection at 254 nm, t_R = 16.27 min, t_S = 18.89 min.

(*R*)-*N*-(1-(2,6-Diiodophenyl)ethyl)picolinamide (12b-(*R*)):



The compound **12b**-(*R*) was obtained as a colourless solid (104 mg, 87%, 0.25 mmol scale).

R_f = 0.6 (EtOAc/hexane = 20:80); mp: 112-114 °C.

IR (DCM): 3382, 1671, 1507 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 9.20 (d, 1H, *J* = 7.3 Hz), 8.60 (d, 1H, *J* = 4.7 Hz), 8.15 (d, 1H, *J* = 7.8 Hz), 7.88-7.79 (m, 3H), 7.43-7.40 (m, 1H), 6.53 (t, 1H, *J* = 7.8 Hz), 5.86-5.79 (m, 1H), 1.66 (d, 3H, *J* = 7.2 Hz).

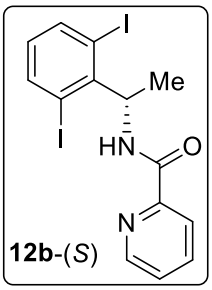
$^{13}C\{^1H\}$ NMR (~101 MHz, $CDCl_3$): δ = 162.9, 149.5, 148.1, 143.1, 142.3, 140.4, 137.2, 130.1, 126.1, 122.2, 57.2, 18.2.

HRMS (ESI): *m/z* $[M+H]^+$ calcd for $C_{14}H_{13}I_2N_2O$: 478.9117; found: 478.9114.

$[\alpha]^{25}_D$ = -274.6 (*c* = 0.05, $CHCl_3$).

The enantiomeric excess (*ee* 95%) of compound **12b**-(*R*) was determined by HPLC using the Daicel Chiralcel OD-H column, hexane/*i*-PrOH 90:10, flow rate 1.0 mL/min, UV detection at 254 nm, t_R = 16.90 min, t_S = 19.64 min.

(*S*)-*N*-(1-(2,6-Diiodophenyl)ethyl)picolinamide (12b-(*S*)):



The compound **12b**-(*S*) was obtained as a colourless solid (106 mg, 89%, 0.25 mmol scale).

R_f = 0.6 (EtOAc/hexane = 20:80); mp: 112-114 °C.

IR (DCM): 3384, 1673, 1505 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 9.20 (d, 1H, *J* = 7.3 Hz), 8.60 (d, 1H, *J* = 4.8 Hz), 8.15 (d, 1H, *J* = 7.8 Hz), 7.88-7.79 (m, 3H), 7.44-7.40 (m, 1H), 6.54 (t, 1H, *J* = 7.8 Hz), 5.86-5.79 (m, 1H), 1.66 (d, 3H, *J* = 7.2 Hz).

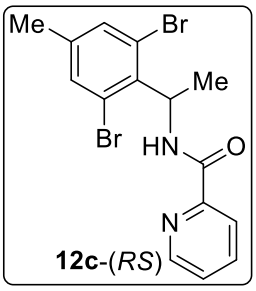
$^{13}C\{^1H\}$ NMR (~101 MHz, $CDCl_3$): δ = 162.9, 149.5, 148.1, 143.1, 142.3, 140.4, 137.2, 130.1, 126.1, 122.2, 57.2, 18.1.

HRMS (ESI): *m/z* $[M+H]^+$ calcd for $C_{14}H_{13}I_2N_2O$: 478.9117; found: 478.9128.

$[\alpha]^{25}_D$ = +274.2 (*c* = 0.05, $CHCl_3$).

The enantiomeric excess (*ee* 96%) of compound **12b**-(*S*) was determined by HPLC using the Daicel Chiralcel OD-H column, hexane/*i*-PrOH 90:10, flow rate 1.0 mL/min, UV detection at 254 nm, t_R = 16.89 min, t_S = 19.53 min.

***N*-(1-(2,6-Dibromo-4-methylphenyl)ethyl)picolinamide (12c-(*RS*)):**



The compound **12c**-(*RS*) was obtained as a yellow coloured semi-solid (61 mg, 51%, 0.30 mmol scale).

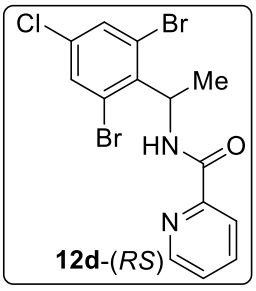
R_f = 0.6 (EtOAc/hexane = 20:80).

IR (DCM): 3383, 1675, 1506 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 9.15 (d, 1H, J = 8.2 Hz), 8.59 (d, 1H, J = 4.7 Hz), 8.16 (d, 1H, J = 7.8 Hz), 7.81 (td, 1H, J_1 = 7.7 Hz, J_2 = 1.0 Hz), 7.43-7.35 (m, 3H), 6.14-6.07 (m, 1H), 2.24 (s, 3H), 1.68 (d, 3H, J = 7.2 Hz).

$^{13}C\{^1H\}$ NMR (~101 MHz, DMSO-d_6): δ = 162.7, 149.5, 149.1, 140.9, 138.5, 136.6, 134.3, 134.0, 127.3, 122.3, 49.9, 19.9, 18.8.

HRMS (ESI): *m/z* $[M+H]^+$ calcd for $C_{15}H_{15}Br_2N_2O$: 396.9551; found: 396.9565.

***N*-(1-(2,6-Dibromo-4-chlorophenyl)ethyl)picolinamide (12d-(*RS*)):**



The compound **12d**-(*RS*) was obtained as a yellow coloured semi-solid (84 mg, 67%, 0.30 mmol scale).

R_f = 0.6 (EtOAc/hexane = 20:80).

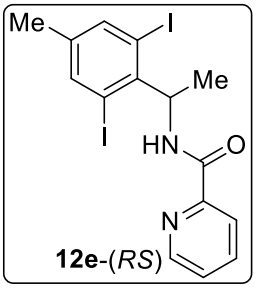
IR (DCM): 3391, 1672, 1508 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 9.10 (d, 1H, J = 8.0 Hz), 8.59 (dd, 1H, J_1 = 4.7 Hz, J_2 = 0.6 Hz), 8.15 (d, 1H, J = 7.8 Hz), 7.83 (td, 1H, J_1 = 7.7 Hz, J_2 = 1.7 Hz), 7.60-7.50 (m, 2H), 7.45-7.41 (m, 1H), 6.10-6.02 (m, 1H), 1.68 (d, 3H, J = 7.2 Hz).

$^{13}C\{^1H\}$ NMR (~101 MHz, $CDCl_3$): δ = 163.2, 149.5, 148.2, 138.3, 137.4, 133.8, 133.4, 132.3, 126.3, 122.4, 49.9, 18.3.

HRMS (ESI): *m/z* $[M+H]^+$ calcd for $C_{14}H_{12}Br_2ClN_2O$: 416.9005; found: 416.9021.

***N*-(1-(2,6-Diiodo-4-methylphenyl)ethyl)picolinamide (12e-(*RS*)):**



The compound **12e**-(*RS*) was obtained as a colourless solid (139 mg, 81%, 0.35 mmol scale).

R_f = 0.6 (EtOAc/hexane = 20:80); mp: 139-141 °C.

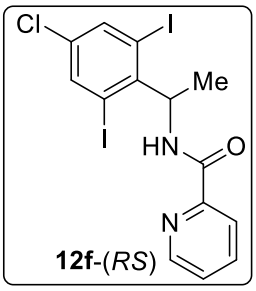
IR (DCM): 3381, 1671, 1506 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 9.15 (d, 1H, J = 7.4 Hz), 8.60 (d, 1H, J = 4.7 Hz), 8.15 (d, 1H, J = 7.8 Hz), 7.83-7.73 (m, 3H), 7.43-7.40 (m, 1H), 5.82-5.75 (m, 1H), 2.18 (s, 3H), 1.65 (d, 3H, J = 7.2 Hz).

$^{13}C\{^1H\}$ NMR (~101 MHz, $CDCl_3$): δ = 163.0, 149.7, 148.2, 143.0, 141.0, 140.3, 140.2, 137.3, 126.1, 122.3, 56.9, 19.5, 18.4.

HRMS (ESI): *m/z* $[M+H]^+$ calcd for $C_{15}H_{15}I_2N_2O$: 492.9274; found: 492.9283.

***N*-(1-(4-Chloro-2,6-diiodophenyl)ethyl)picolinamide (12f-(*RS*)):**



The compound **12f**-(*RS*) was obtained as a colourless solid (119 mg, 78%, 0.30 mmol scale).

R_f = 0.6 (EtOAc/hexane = 20:80); mp: 110-112 °C.

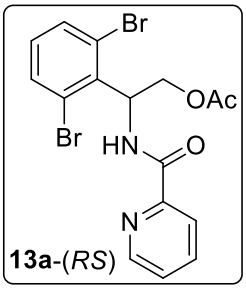
IR (DCM): 3388, 1671, 1502 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 9.11 (d, 1H, J = 6.7 Hz), 8.60 (d, 1H, J = 4.6 Hz), 8.14 (d, 1H, J = 7.8 Hz), 7.90-7.80 (m, 3H), 7.45-7.41 (m, 1H), 5.78-5.70 (m, 1H), 1.64 (d, 3H, J = 7.2 Hz).

$^{13}C\{^1H\}$ NMR (~101 MHz, $CDCl_3$): δ = 163.0, 149.3, 148.2, 141.7, 141.5, 139.5, 137.3, 133.6, 126.2, 122.2, 56.8, 18.0.

HRMS (ESI): *m/z* $[M+H]^+$ calcd for $C_{14}H_{12}ClI_2N_2O$: 512.8728; found: 512.8738.

2-(2,6-Dibromophenyl)-2-(picolinamido)ethyl acetate (13a-(*RS*)):



The compound **13a**-(*RS*) was obtained as a colourless solid (56 mg, 63%, 0.2 mmol scale).

R_f = 0.55 (EtOAc/hexane = 50:50); mp: 80-82 °C.

IR (DCM): 3379, 1745, 1511 cm^{-1}.

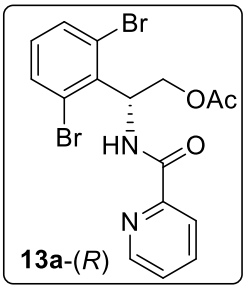
^1H NMR (400 MHz, $CDCl_3$): δ = 9.38 (d, 1H, J = 9.0 Hz), 8.62 (d, 1H, J = 4.7 Hz), 8.17 (d, 1H, J = 7.8 Hz), 7.84 (td, 1H, J_1 = 7.7 Hz, J_2 = 1.6 Hz), 7.59 (br. s, 2H), 7.46-7.43 (m, 1H), 7.00 (t, 1H, J = 8.0 Hz), 6.46-6.40 (m, 1H), 4.83 (dd, 1H, J_1 = 11.2 Hz, J_2 = 8.8 Hz), 4.51 (dd, 1H, J_1 = 11.3 Hz, J_2 = 6.0 Hz), 2.06 (s, 3H).

$^{13}C\{^1H\}$ NMR (~101 MHz, $CDCl_3$): δ = 170.8, 163.9, 149.4, 148.4, 137.3, 135.6, 134.1, 133.1, 130.3, 126.3, 122.4, 63.0, 53.5, 20.8.

HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{16}H_{15}Br_2N_2O_3$: 440.9449; found: 440.9429.

The HPLC of compound **13a**-(*RS*) was determined by using the Daicel Chiralcel OJ column, hexane/*i*-PrOH 90:10, flow rate 1.0 mL/min, UV detection at 254 nm, t_S = 31.20 min, t_R = 26.99 min.

(*R*)-2-(2,6-Dibromophenyl)-2-(picolinamido)ethyl acetate (13a-(*R*)):



The compound **13a**-(*R*) was obtained as a colourless solid (58 mg, 66%, 0.2 mmol scale).

R_f = 0.55 (EtOAc/hexane = 50:50); mp: 82-84 °C,

IR (DCM): 3379, 1745, 1511 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 9.38 (d, 1H, J = 9.0 Hz), 8.62 (d, 1H, J = 4.6 Hz), 8.17 (d, 1H, J = 7.8 Hz), 7.84 (t, 1H, J = 7.7 Hz), 7.57 (br. s, 2H), 7.46-7.43 (m, 1H), 7.00 (t, 1H, J = 8.0 Hz), 6.45-6.39 (m, 1H), 4.83 (dd, 1H, J_1 = 11.2 Hz, J_2 = 8.9 Hz), 4.50 (dd, 1H, J_1 = 11.3 Hz, J_2 = 6.0 Hz), 2.06 (s, 3H).

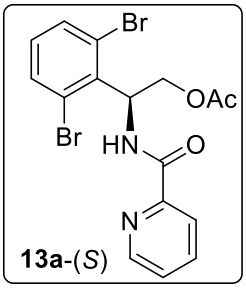
$^{13}C\{^{1}H\}$ NMR (~101 MHz, $CDCl_3$): δ = 170.9, 163.9, 149.4, 148.4, 137.3, 135.6, 134.1, 133.0, 130.3, 126.4, 122.4, 63.0, 53.4, 20.8.

HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{16}H_{15}Br_2N_2O_3$: 440.9449; found: 440.9429.

$[\alpha]^{25}_D$ = 170.0 (*c* = 0.02, $CHCl_3$).

The enantiomeric excess (*ee* >98%) of compound **13a**-(*R*) was determined by HPLC using the Daicel Chiralcel OJ column, hexane/*i*-PrOH 90:10, flow rate 1.0 mL/min, UV detection at 254 nm, t_S = not detected min, t_R = 27.36 min.

(*S*)-2-(2,6-Dibromophenyl)-2-(picolinamido)ethyl acetate (13a-(*S*)):



The compound **13a**-(*S*) was obtained as a colourless solid (56 mg, 64%, 0.2 mmol scale).

R_f = 0.55 (EtOAc/hexane = 50:50); mp: 82-84 °C.

IR (DCM): 3376, 1742, 1507 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.38 (d, 1H, *J* = 8.9 Hz), 8.62 (d, 1H, *J* = 4.6 Hz), 8.17 (d, 1H, *J* = 7.8 Hz), 7.84 (t, 1H, *J* = 7.6 Hz), 7.58 (br. s, 2H), 7.46-7.43 (m, 1H), 7.00 (t, 1H, *J* = 8.0 Hz), 6.46-6.40 (m, 1H), 4.83 (dd, 1H, J_1 = 11.1 Hz, J_2 = 9.0 Hz), 4.51 (dd, 1H, J_1 = 11.3 Hz, J_2 = 6.0 Hz), 2.06 (s, 3H).

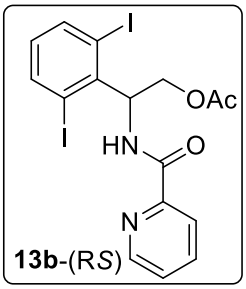
$^{13}C\{^{1}H\}$ NMR (~101 MHz, $CDCl_3$): δ = 170.9, 163.9, 149.4, 148.4, 137.3, 135.6, 134.1, 133.0, 130.3, 126.4, 122.4, 63.0, 53.5, 20.8.

HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{16}H_{15}Br_2N_2O_3$: 440.9449; found: 440.9434.

$[\alpha]^{25}_D$ = -102.0 (*c* = 0.02, $CHCl_3$).

The enantiomeric excess (*ee* >98%) of compound **13a**-(*S*) was determined by HPLC using the Daicel Chiralcel OJ column, hexane/*i*-PrOH 90:10, flow rate 1.0 mL/min, UV detection at 254 nm, t_S = 32.54 min, t_R = 28.89 min.

2-(2,6-Diiodophenyl)-2-(picolinamido)ethyl acetate (13b-(*RS*)):



The compound **13b**-(*RS*) was obtained as a yellow coloured solid (90 mg, 84%, 0.2 mmol scale).

R_f = 0.60 (EtOAc/hexane = 50:50); mp: 120-122 °C.

IR (DCM): 3367, 1739, 1504 cm^{-1}.

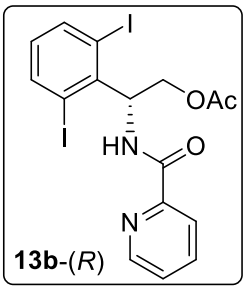
^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.43 (d, 1H, *J* = 8.0 Hz), 8.64 (d, 1H, *J* = 4.6 Hz), 8.17 (d, 1H, *J* = 7.8 Hz), 7.96-7.82 (m, 3H), 7.47-7.44 (m, 1H), 6.61 (t, 1H, *J* = 7.8 Hz), 6.16-6.10 (m, 1H), 4.85 (t, 1H, *J* = 10.7 Hz), 4.46 (dd, 1H, J_1 = 11.4 Hz, J_2 = 5.8 Hz), 2.09 (s, 3H).

$^{13}C\{^{1}H\}$ NMR (~101 MHz, $CDCl_3$): δ = 170.9, 163.7, 149.3, 148.4, 142.5, 140.7, 139.5, 137.3, 130.9, 126.3, 122.4, 62.9, 60.4, 20.9.

HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{16}H_{15}I_2N_2O_3$: 536.9172; found: 536.9191.

The HPLC of compound **13b**-(*RS*) was determined by using the Daicel Chiralcel OD column, hexane/*i*-PrOH 95:05, flow rate 1.0 mL/min, UV detection at 254 nm, t_S = 32.51 min, t_R = 28.24 min.

(*R*)-2-(2,6-Diiodophenyl)-2-(picolinamido)ethyl acetate (13b-(*R*)):



The compound **13b**-(*R*) was obtained as a yellow coloured solid (95 mg, 89%, 0.2 mmol scale).

R_f = 0.60 (EtOAc/hexane = 50:50); mp: 123-125 °C.

IR (DCM): 3367, 1739, 1504 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 9.43 (d, 1H, *J* = 8.0 Hz), 8.64 (d, 1H, *J* = 4.7 Hz), 8.17 (d, 1H, *J* = 7.8 Hz), 7.96-7.82 (m, 3H), 7.47-7.44 (m, 1H), 6.61 (t, 1H, *J* = 7.8 Hz), 6.16-6.10 (m, 1H), 4.85 (t, 1H, *J* = 11.0 Hz), 4.46 (dd, 1H, J_1 = 11.4 Hz, J_2 = 5.8 Hz), 2.09 (s, 3H).

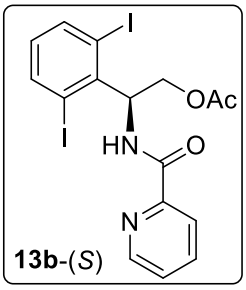
$^{13}C\{^1H\}$ NMR (~101 MHz, $CDCl_3$): δ = 170.9, 163.7, 149.3, 148.4, 142.5, 140.7, 139.5, 137.3, 130.9, 126.3, 122.4, 62.9, 60.4, 20.9.

HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{16}H_{15}I_2N_2O_3$: 536.9172; found: 536.9193.

$[\alpha]^{25}_D$ = 205.7 (*c* = 0.06, $CHCl_3$).

The enantiomeric excess (*ee* >98%) of compound **13b**-(*R*) was determined by HPLC using the Daicel Chiralcel OD column, hexane/*i*-PrOH 95:05, flow rate 1.0 mL/min, UV detection at 254 nm, t_S = not detected min, t_R = 29.00 min.

(*S*)-2-(2,6-Diiodophenyl)-2-(picolinamido)ethyl acetate (13b-(*S*)):



The compound **13b**-(*S*) was obtained as a yellow coloured solid (90 mg, 84%, 0.2 mmol scale).

R_f = 0.60 (EtOAc/hexane = 50:50); mp: 122-124 °C.

IR (DCM): 3367, 1739, 1504 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 9.43 (d, 1H, *J* = 8.0 Hz), 8.63 (d, 1H, *J* = 4.6 Hz), 8.16 (d, 1H, *J* = 7.8 Hz), 7.96-7.82 (m, 3H), 7.46-7.43 (m, 1H), 6.60 (t, 1H, *J* = 7.8 Hz), 6.15-6.10 (m, 1H), 4.87-4.82 (m, 1H), 4.45 (dd, 1H, J_1 = 11.4 Hz, J_2 = 5.8 Hz), 2.09 (s, 3H).

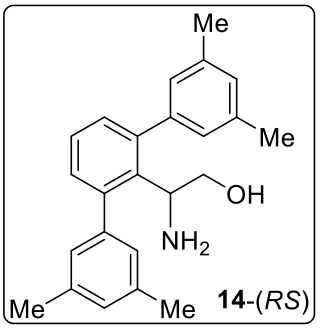
$^{13}C\{^1H\}$ NMR (~101 MHz, $CDCl_3$): δ = 170.9, 163.7, 149.3, 148.4, 142.5, 140.7, 139.5, 137.3, 130.9, 126.3, 122.4, 62.9, 60.4, 20.9.

HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{16}H_{15}I_2N_2O_3$: 536.9172; found: 536.9197.

$[\alpha]^{25}_D$ = -181.6 (*c* = 0.06, $CHCl_3$).

The enantiomeric excess (*ee* >98%) of compound **13b**-(*S*) was determined by HPLC using the Daicel Chiralcel OD column, hexane/*i*-PrOH 95:05, flow rate 1.0 mL/min, UV detection at 254 nm, t_S = 30.12 min, t_R = 27.01 min.

2-Amino-2-(3,3'',5,5''-tetramethyl-[1,1':4',1''-terphenyl]-2'-yl)ethan-1-ol (14-(*RS*)):



The compound **14**-(*RS*) was obtained from procedure H after purification by column chromatography on silica gel (MeOH:DCM = 10:90) as a colourless solid (50 mg, 61%, 0.24 mmol scale).

R_f = 0.40 (MeOH:DCM = 10:90); mp: 198-200 ^oC.

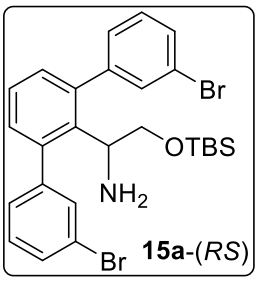
IR (DCM): 3012, 2357, 1599 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.28-7.24 (m, 1H), 7.14 (d, 2H, J = 7.5 Hz), 7.03 (br. s, 2H), 6.96 (br. s, 4H), 4.10-4.07 (m, 1H), 3.49 (dd, 1H, J_1 = 10.5 Hz, J_2 = 4.6 Hz), 3.41 (t, 1H, J = 10.3 Hz), 2.38 (s, 12H), 1.78 (br. s, 2H).

$^{13}C\{^1H\}$ NMR (~101 MHz, $CDCl_3$): δ = 142.7, 142.2, 137.6, 130.4, 128.9, 127.3, 125.7, 66.9, 55.9, 21.4.

HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{24}H_{28}NO$: 346.2171; found: 346.2164.

2-((*Tert*-butyldimethylsilyl)oxy)-1-(3,3''-dibromo-[1,1':3',1''-terphenyl]-2'-yl)ethan-1-amine (15a-(*RS*)):



The compound **15a**-(*RS*) was obtained as a colourless liquid (46 mg, 63%, 0.13 mmol scale).

R_f = 0.35 (EtOAc:Hexane = 20:80).

IR (DCM): 2954, 1599, 1090 cm^{-1}.

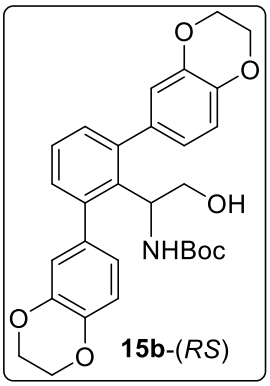
^1H NMR (400 MHz, $CDCl_3$): δ = 7.60 (s, 2H), 7.54-7.52 (m, 2H), 7.37-7.35 (m, 2H), 7.31-7.27 (m, 3H), 7.16 (d, 2H, J = 7.5 Hz), 4.07 (dd, 1H, J_1 = 9.2, J_2 = 5.1 Hz), 3.43 (dd, 1H, J_1 = 9.9, J_2 = 5.2 Hz), 3.36 (t, 1H, J = 9.7 Hz), 1.50 (s, 2H), 0.78 (s, 9H), -0.09 (s, 3H), -0.12 (s, 3H).

$^{13}C\{^1H\}$ NMR (~101 MHz, $CDCl_3$): δ = 144.5, 141.5, 137.0, 132.7, 130.8, 130.3, 129.4, 128.4, 126.1, 122.1, 67.9, 55.8, 25.9, 18.3, -5.4, -5.5.

HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{26}H_{32}Br_2NOSi$: 560.0620; found: 560.0609.

Under the reaction conditions in which **15a**-(*RS*) was obtained, **15a**-(*R*) was also prepared and the NMR spectra of **15a**-(*R*) has been given in the supporting information. However, the HPLC pattern/enantiopurity could not be determined, thus the characterization data was not provided.

***Tert*-butyl (1-(2,6-bis(2,3-dihydrobenzo[*b*][1,4]dioxin-6-yl)phenyl)-2-hydroxyethyl)carbamate (15b-(*RS*)):**



The compound **15b**-(*RS*) was obtained (from procedures J and K) as a red coloured solid (35 mg, 53%, 0.13 mmol scale).

R_f = 0.5 (EtOAc/hexane = 50:50); mp: 176-178 ^oC.

IR (DCM): 3428, 1706, 1508 cm^{-1}.

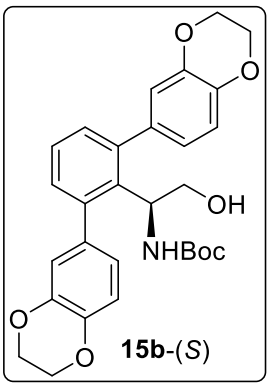
^1H NMR (400 MHz, $CDCl_3$): δ = 7.22 (d, 1H, J = 7.2 Hz), 7.12 (d, 2H, J = 7.5 Hz), 6.91-6.81 (m, 6H), 5.14-5.08 (m, 1H), 4.46 (br. s, 1H), 4.29 (s, 8H), 3.54 (s, 2H), 1.37 (s, 9H).

$^{13}C\{^1H\}$ NMR (~101 MHz, $CDCl_3$): δ = 155.5, 143.1, 143.0, 141.9, 135.1, 134.7, 130.8, 126.3, 122.5, 118.4, 116.9, 79.2, 66.8, 64.4, 55.5, 28.3.

HRMS (ESI): *m/z* $[M+Na]^+$ calcd for $C_{29}H_{31}NNaO_7$: 528.1998; found 528.1998.

The HPLC of compound **15b**-(*RS*) was determined by using the Daicel Chiralcel OD-H column, hexane/i-PrOH 70:30, flow rate 1.0 mL/min, UV detection at 254 nm, t_S = 10.36 min, t_R = 6.13 min.

(*S*)-*Tert*-butyl (1-(2,6-bis(2,3-dihydrobenzo[*b*][1,4]dioxin-6-yl)phenyl)-2-hydroxyethyl)carbamate (15b-(*S*)):



The compound **15b**-(*S*) was obtained (from procedures J and K) as a red coloured solid (76 mg, 56%, 0.27 mmol scale).

R_f = 0.5 (EtOAc/hexane = 50:50); mp: 177-179 ^oC.

IR (DCM): 3432, 1707, 1505 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.22 (d, 1H, J = 7.5 Hz), 7.12 (d, 2H, J = 7.5 Hz), 6.91-6.81 (m, 6H), 5.13-5.07 (m, 1H), 4.46 (br. s, 1H), 4.28 (s, 8H), 3.53 (s, 2H), 1.37 (s, 9H).

$^{13}C\{^1H\}$ NMR (~101 MHz, $CDCl_3$): δ = 155.5, 143.0, 143.0, 141.9, 135.1, 134.7, 130.8, 126.3, 122.5, 118.4, 116.9, 79.2, 66.7, 64.4, 55.5, 28.3.

HRMS (ESI): *m/z* $[M+Na]^+$ calcd for $C_{29}H_{31}NNaO_7$: 528.1998; found 528.1998.

$[\alpha]^{25}_D$ = +25.0 (c = 0.04, $CHCl_3$).

The enantiomeric excess (*ee* 93%) of compound **15b**-(*S*) was determined by HPLC using the Daicel Chiralcel OD-H column, hexane/*i*-PrOH 70:30, flow rate 1.0 mL/min, UV detection at 254 nm, t_S = 10.47 min, t_R = 5.99 min.

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Chapter 3

Pd-Catalyzed Arylation and Benzylation of Tyrosine at the δ-C(sp^2)-H and C(2) Positions: Expanding the Library of Unnatural Tyrosines

For the purpose of this thesis work, the work of chapter 3 is adapted with permission from the publication; Singh, P .; Babu. S. A.* *Eur. J. Org. Chem*. **2023**, e202300440. Title: Pd-Catalyzed Arylation and Benzylation of Tyrosine at the δ-C(sp^2)-H and C(2) Positions: Expanding the Library of Unnatural Tyrosines

In recent years, the C-H functionalization of aliphatic and aromatic organic molecules and bioactive frameworks have gained paramount importance in organic chemistry.[1-3] The Pd(II)-catalyzed bidentate directing group-assisted site-selective installation of functional groups in different classes of organic compounds including amino acids is a powerful strategy for expanding their corresponding libraries.[2,3] Unnatural amino acid derivatives are highly sought-after compounds in organic chemistry, chemical biology and drug discovery.[4] Arylated amino acid and biaryl-based amino acid scaffolds are prevalent in natural products, bioactive small organic molecules and peptides.[5] The synthesis of biaryl amino acid derivatives has been accomplished by traditional cross-coupling[6] and lately *via* the C-H functionalization method.[3] In particular interest, tyrosine motifs are core structures in natural products (e.g., alkaloids and peptides, Figure 1) and medicinal compounds (e.g., saframycin A (an anticancer agent)).[5-8] Tyrosine motif is used as a probing tool in chemical biology and it is also an attractive target for post-translational modification in peptides and proteins due to its phenolic unit.[9] Furthermore, tyrosine-based biaryls have received special attention in chemical biology. Some peptides and proteins incorporate cross-linked tyrosine (biaryl unit type) residues in their structures, which impart interesting properties to the modified peptides.[6a,10]

Owing to their importance, there has been a vested interest in developing methods for the synthesis of modified tyrosines *via* different routes[6-9] including the C-H functionalization method.[11-16] The expansion of libraries of tyrosine congeners such as phenylalanine and phenylglycine has been explored *via* the Pd-catalyzed C(2)-H functionalization (*viz.* δ-(sp^2)-H (*ortho*) arylation, benzylation, etc).[17] Compared with its congener phenylalanine, the intermolecular arylation and benzylation of the C(2) position in the aryl ring of tyrosine derivatives are yet to be explored.[3g, h] Considering the importance of tyrosine derivatives and biaryl amino acids,[5] the arylation and benzylation of C(2) position of tyrosine derivatives

would be a valuable effort towards enriching the tyrosine library with biaryl or terphenyl and diarylmethane-based tyrosine derivatives.

With regard to the developments using the bidentate directing group (DG)-directed C-H functionalization tactic, in aromatic amine substrates such as benzylamine or phenylglycine, the *ortho* C-H bond is referred to as γ-C(sp^2)-H bond with respect to the amine moiety.[2,18] In general, the bidentate DG (e.g., picolinamide moiety) directed C-H functionalization of the γ-C-H bond in a benzylamine type substrate is believed to undergo *via* a favored 5-membered metallacycle intermediate.[2,3,18] Along this line, the *ortho* / C(2)-H bond in tyrosine (similar to phenylalanine / phenethylamine systems) is referred to as a remote δ-C(sp^2)-H bond with respect to the amine moiety.[2,3,17,19] Accordingly, the bidentate DG (e.g., picolinamide moiety) directed C-H functionalization of the δ-C-H bond in a phenethylamine type substrate is believed to undergo *via* a 6-membered metallacycle intermediate.[2,3,16,17,19]

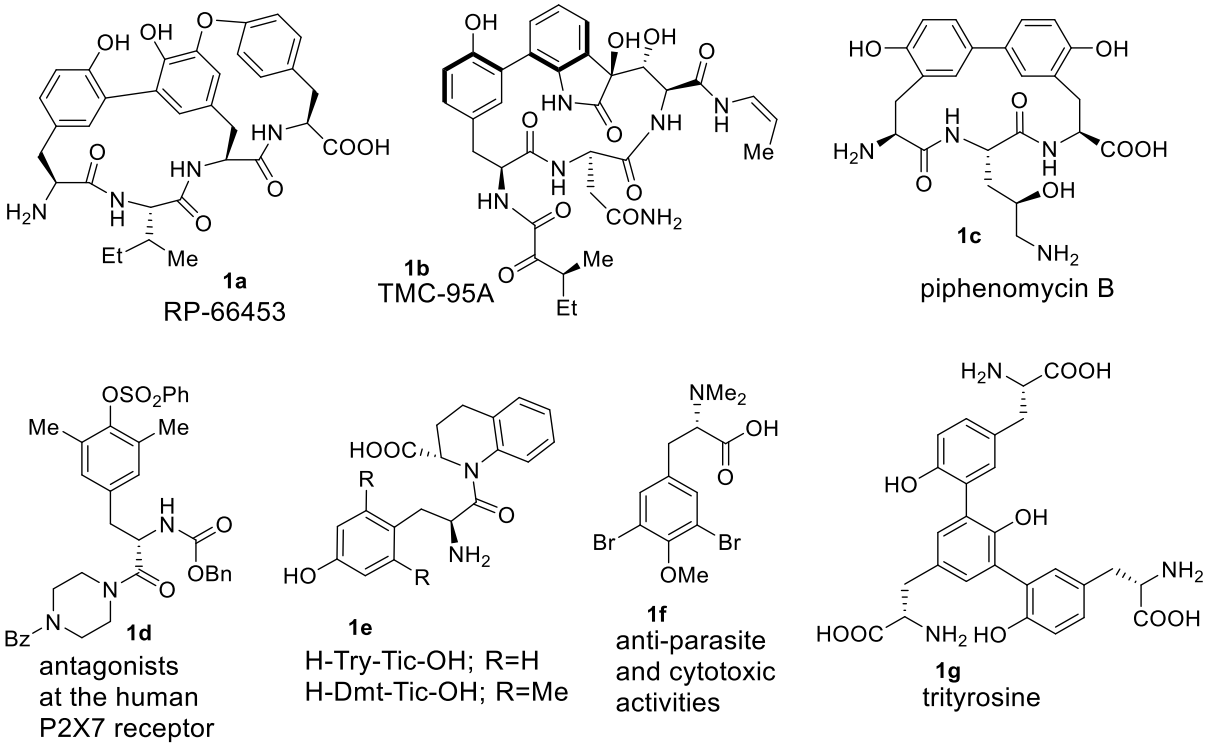
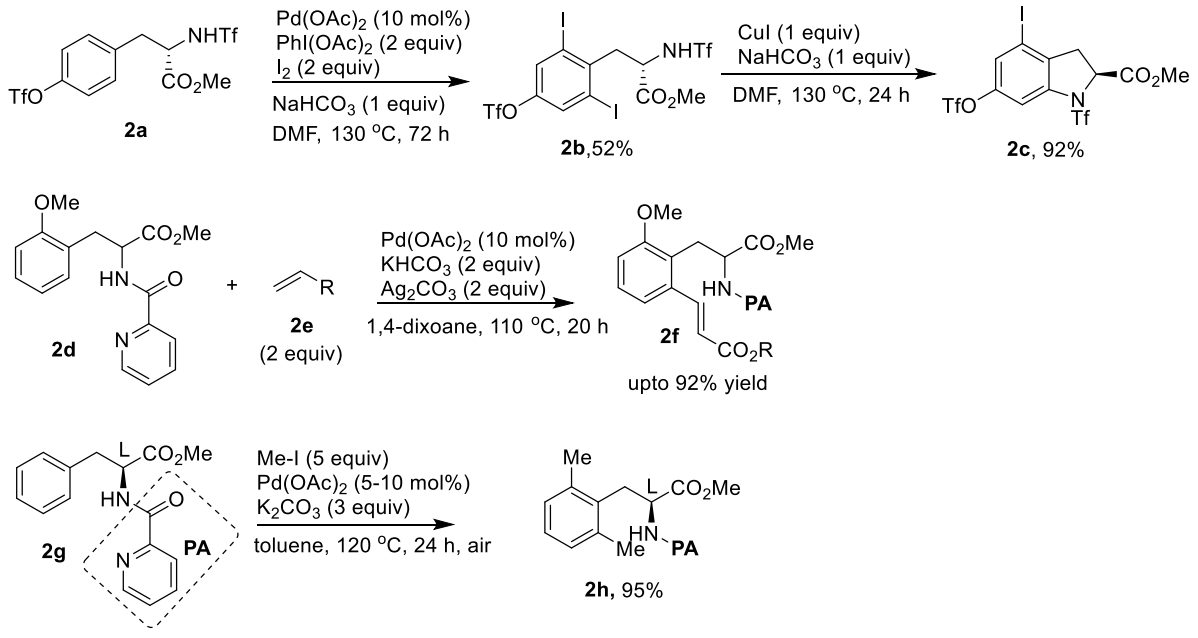


Figure 1. Example of bioactive tyrosine and biaryl-based tyrosine molecules.

Encouraged by the importance and application of tyrosine scaffolds we envisioned to functionalize tyrosine motifs *via* an efficient and regioselective C-H functionalization strategy. In this context, in the next section, we will present some of the available literature reports for tyrosine *via* C-H functionalization route.

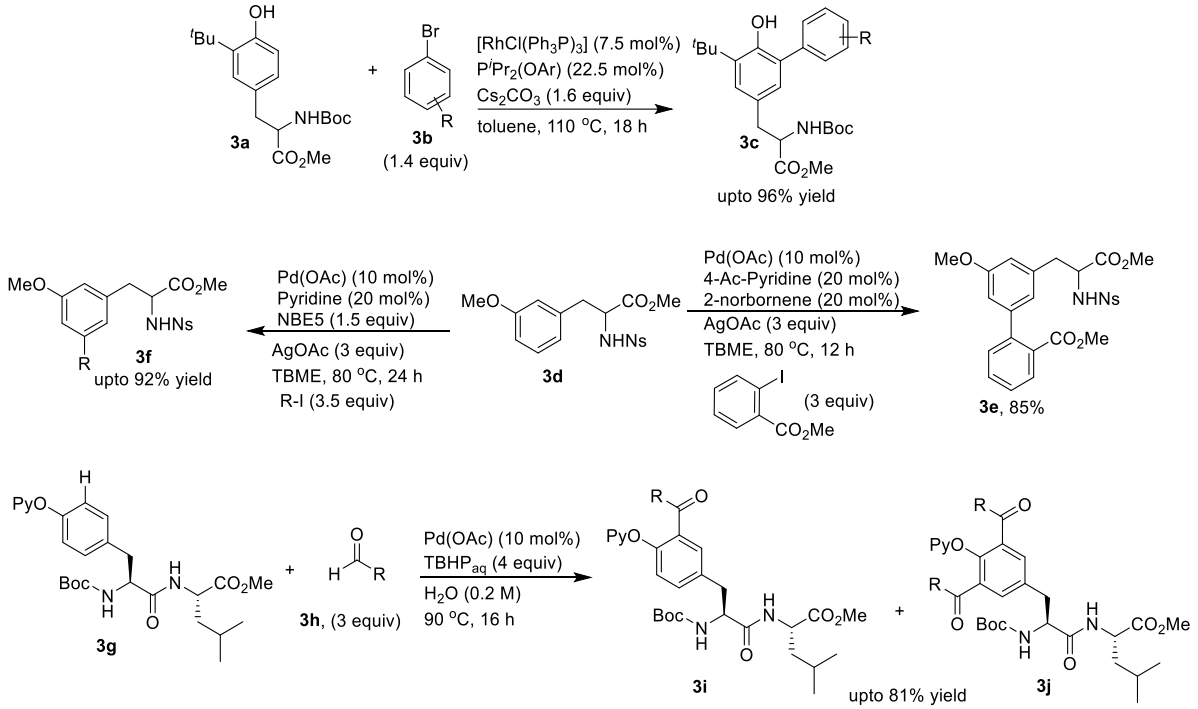
Selected Literature reports dealing with C(2)-H functionalization of tyrosine: Yu and co-workers in 2008[12d], reported the facile synthesis of indolines *via* Palladium-catalyzed C-H iodination of tyrosine followed by CuI promoted intramolecular amination reaction (scheme 1a). Zhao's group in 2017[12a] reported palladium-catalyzed picolinamide aided *ortho* C-H olefination of tyrosine. The optimized reaction condition for olefination requires substrate **2d** (1 equiv), $Pd(OAc)_2$ (10 mol%), $KHCO_3$ (2 equiv), Ag_2CO_3 (2 equiv) in 1,4-dioxane as a solvent at 110 ^oC for 20 h under nitrogen atm to give C-H olefinated product **2f** in good to excellent yield. The reaction condition works well for a variety of substrates with a wide range of functional group tolerance (Scheme 1a). In 2017[16], Ma's group reported picolinamide directed a simple and efficient approach for *ortho*-C-H methylation of (*S*)-tyrosine moiety. The reaction method utilizes substrate **2g** (1 equiv), $Pd(OAc)_2$ (5 mol%), Me-I (5 equiv), and K_2CO_3 (3 equiv) in toluene at 120 ^oC for 24 h under air to accomplish the desired methylated product **2h** in 95% yield (Scheme 1a).



Scheme 1a: Representative examples dealing with C(2)-H functionalization of tyrosine.

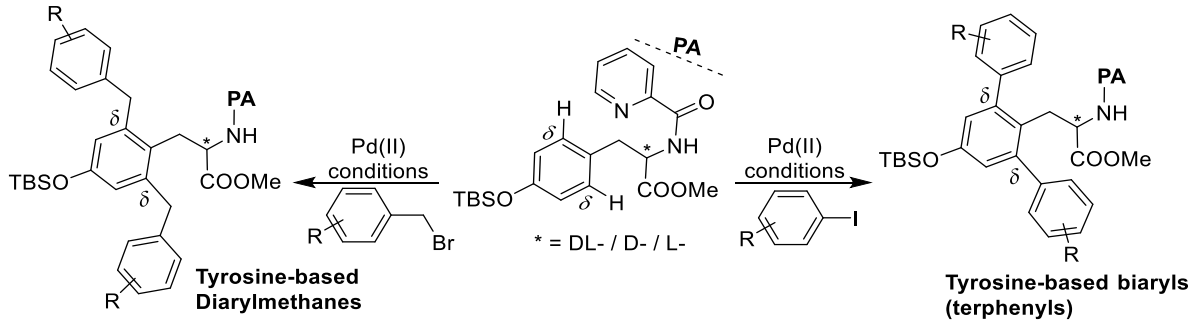
Selected Literature reports related to C(3)-H functionalization of tyrosine: Mitchell's group in 2009[11a] introduced rhodium-catalyzed C(3)-H arylation of protected racemic 2-*tert*-butyl tyrosine **3a** using aryl-bromide **3b** as a coupling partner. Authors have further elaborated this protocol for obtaining di-arylated tyrosine by removal of the *tert*-butyl group after the first arylation (Scheme 1b). On the same line, Yu's group in 2017[11b] disclosed a palladium-catalyzed approach for C(3)-H arylation of nosyl-protected tyrosine using a combination of 2-

norbornene and pyridine-based ligands. The arylation reaction condition utilizes substrate **3d** (1 equiv), $Pd(OAc)_2$ (10 mol%), AgOAc (3 equiv), 2-norbornene (20 mol%), 4-Ac-pyridine (20 mol%) in TBME as a solvent at 80 °C for 12 h to give corresponding C(3)-H arylated product **3e** in 85% yield (Scheme 1b). Following the same concept Ding and co-works in 2018[11h] revealed a palladium-catalyzed approach for C(3)-H alkylation of nosyl-protected tyrosine. The reaction works well for a variety of substrates with a wide range of alkyl iodide scope (Scheme 1b). For the first time in 2020[11c], Correa's group reported Pd-catalyzed C-H acylation of tyrosine-containing peptides with aldehydes. The developed method works in an aqueous medium with high functional group tolerance and broad substrate scope. It also offers simple access to a wide range of oligopeptides with transformed side-chain structures, including analogues of neuromedin N and endomorphin-2 (Scheme 1b).



Scheme 1b: representative examples dealing with C(3)-H functionalization of tyrosine.

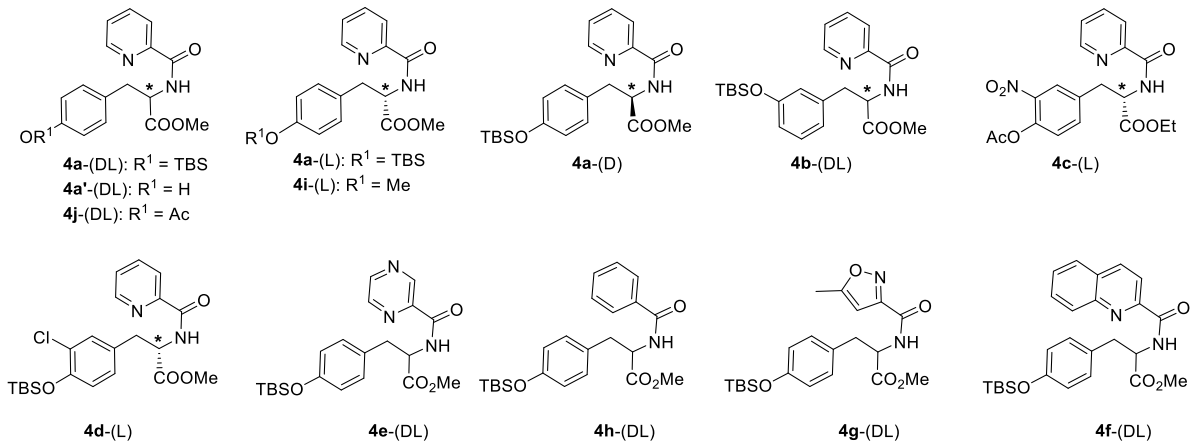
Apart from these limited reports, the remote δ-C(sp^2)-H (*ortho*) arylation and benzylation of the C(2) position of the aryl ring in tyrosine derivatives have not been explored. This paper describes the Pd(II)-catalyzed picolinamide DG-directed arylation and benzylation of the remote δ-C(sp^2)-H bond (C(2) position) of the aryl ring in tyrosine derivatives and assembling of various racemic and enantiopure biaryl- or terphenyl and diarylmethane-based tyrosine motifs (Scheme 1c).



Scheme 1c: Theme of the work

Results and Discussion:

To commence our investigations on the Pd(II)-catalyzed, *ortho* / C(2)-H arylation and benzylation of tyrosines, initially, we prepared racemic and enantiopure OTBS-protected tyrosine substrates 4a-(DL), 4a-(L), 4a-(D), possessing the picolinamide directing group (DG) under the standard procedures.[2,16-19] Then, OTBS-protected *meta* tyrosine substrate 4b-(DL), OTBS-protected tyrosine substrates 4e-(DL), 4f-(DL), 4g-(DL), 4h-(DL), possessing other directing groups were prepared. Next, OAc-protected tyrosine substrate 4c-(L) with a nitro group at the *ortho* position with respect to the OAc group, OTBS-protected tyrosine substrate 4d-(L) with a Cl group at the *ortho* position with respect to the OTBS group and OMe tyrosine substrate 4i-(L) were assembled (Scheme 2). Additionally, tyrosine substrate 4a′-(DL) possessing the free OH group and OAc-protected tyrosine substrate 4j-(DL) were prepared.

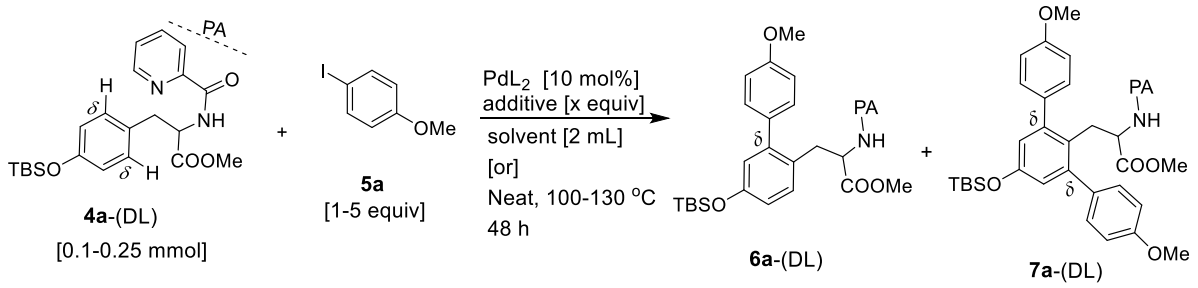


Scheme 2: Tyrosine substrates studied in this work.

Table 1 reveals the screening of conditions for accomplishing the C(2)-H arylation of the aryl ring in tyrosine **4a**-(DL) with *p*-anisyl iodide (**5a**) under the standard Pd(II)-catalyzed

picolinamide-directed *ortho* C-H arylation conditions employed by various groups (*viz.* Daugulis, Chen, Jiang, Zhao, and our group).[2,3,17-20] A silver salt (e.g., AgOAc, Ag_2CO_3) or alkali metal salt is commonly employed as the halide ion (e.g. iodide anion) scavenger to regenerate the Pd(II) catalyst in the proposed bidentate DG-assisted Pd^{II}-Pd^{IV} catalytic cycle.[2,3,17-20] The C(2)-H arylation of tyrosine **4a**-(DL) with **5a** in the presence of the $Pd(OAc)_2$ catalyst (10 mol%) and AgOAc or Ag_2CO_3 additive was performed in different solvents at 110 ^oC for 48 h (entries 1-4, Table 1). These trial reactions are expected to afford the bis C(2) arylated tyrosine-based terphenyl motif **7a**-(DL) and mono C(2) arylated tyrosine-based biaryl motif **6a**-(DL). The reaction conditions of entries 1-4 selectively gave the bis C(2) arylated product **7a**-(DL) in 25-73% yields. The other expected mono C(2)-H arylated product **6a**-(DL) was not obtained in these trials (Table 1). We then tried the Pd(II)-catalyzed C(2)-H arylation of **4a**-(DL) with **5a** in neat condition at 110 to 130 ^oC without using any solvent. These attempts yielded the bis C(2) arylated product **7a**-(DL) in 68-78% yields and the mono C(2)-H arylated product **6a**-(DL) was not obtained in these trials (entries 5, 6, Table 1). Then, to find out a suitable condition to obtain the mono C(2) arylated product **6a**-(DL), we performed the Pd(II)-catalyzed C(2)-H arylation of **4a**-(DL) by using 1 or 3 equiv **5a** in neat condition. While the reaction in which we used 3 equiv of **5a** afforded only the product **7a**-(DL) in 46% yield. On the other hand, the reaction in which we used 1 equiv of **5a** yielded the product **7a**-(DL) in 8% yield and also the mono C(2) arylated product **6a**-(DL) in 18% yield (entries 7,8, Table 1). The reaction of **4a**-(DL) with **5a** (5 equiv) by using a lesser amount of AgOAc (1 equiv) yielded both **7a**-(DL) (37%) and **6a**-(DL) (38%) (entry 9, Table 1). Another attempt involving a reaction of **4a**-(DL) with **5a** by using 0.5 equiv AgOAc yielded both **7a**-(DL) (14%) and **6a**-(DL) (25%) (entry 10, Table 1). Next, we performed the arylation of **4a**-(DL) by using 5 mol% of $Pd(OAc)_2$ (instead of 10 mol%), which yielded both **7a**-(DL) (67%) and **6a**-(DL) (15%) (entry 11, Table 1). We then tried the arylation of **4a**-(DL) with **5a** (5 equiv) by using $Pd(OAc)_2$ (10 mol%) and AgOAc (2.2 equiv) in 24 or 12 h (instead of 48 h). These trials gave both **7a**-(DL) in 70-72% yields and **6a**-(DL) in 8-13% yields (entries 12,13, Table 1). Furthermore, we tried the arylation of **4a**-(DL) with **5a** (5 equiv) by using $Pd(OAc)_2$ (10 mol%) and AgOAc (2.2 equiv) at 60 ^oC instead of 130 ^oC. This trial gave both **7a**-(DL) (59%) and **6a**-(DL) (23%) (entry 14, Table 1).

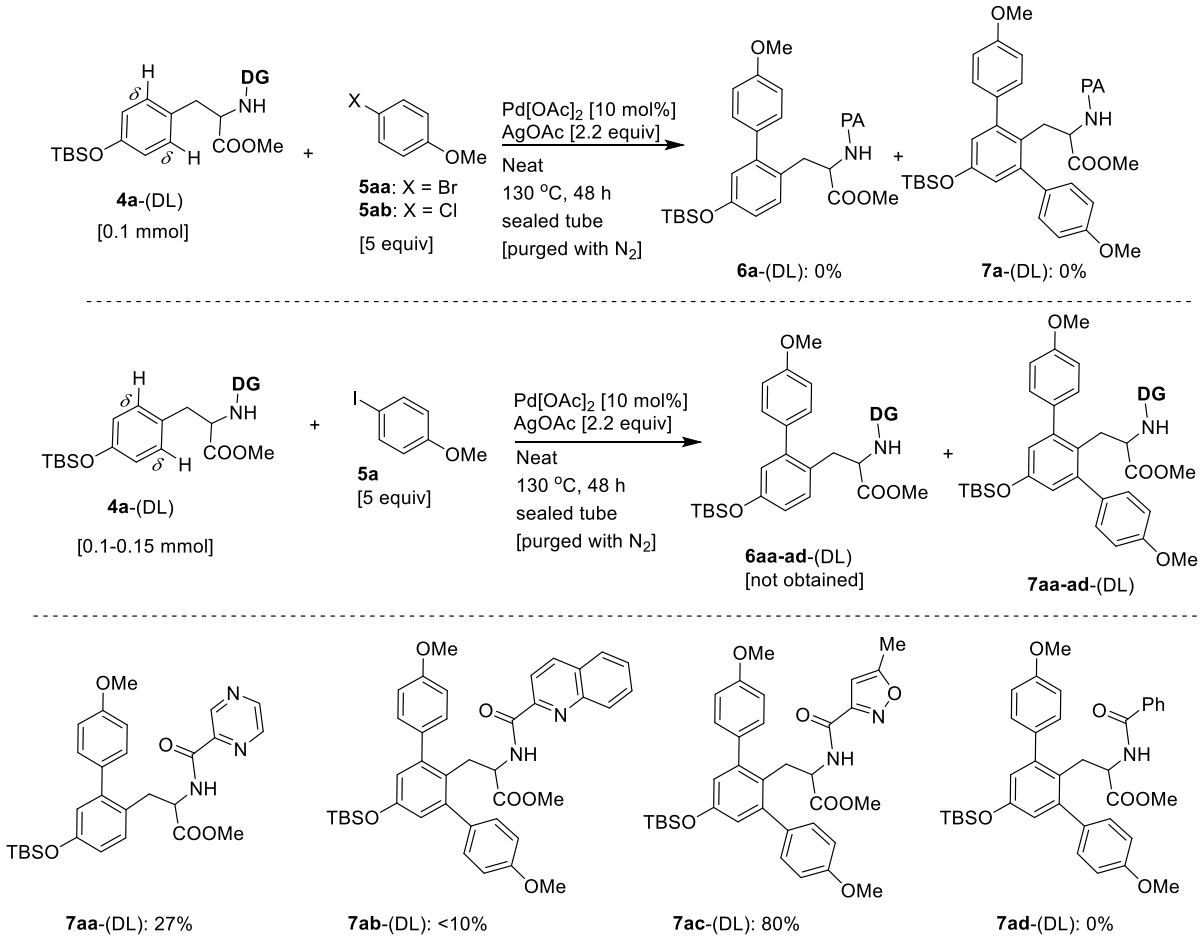
Optimization table 1: Screening of reaction condition for C(2)-H arylation of tyrosine **4a**-(DL).



Entry	PdL_2 [10mol%]	5a [equiv]	additives [equiv]	solvent	T [°C]	Time [h]	6a[DL]: yield [%]	7a[DL]: yield [%]
1[a]	$Pd[OAc]_2$	5	AgOAc [2.2 equiv]	*t*-amylOH	110	48	-	35
2[a]	$Pd[OAc]_2$	5	Ag_2CO_3 [2.5 equiv]	1,4-dioxane	110	48	-	35
3[a]	$PdCl_2$	5	AgOAc [2.2 equiv]	toluene	110	48	-	25
4[b]	$Pd[OAc]_2$	5	Ag_2CO_3 [2.5 equiv]	*t*-amylOH	130	48	-	73
5[b]	$Pd[OAc]_2$	5	Ag_2CO_3 [2.5 equiv]	neat	110	48	-	68
6[b]	$Pd[OAc]_2$	**5**	**AgOAc [2.2 equiv]**	**neat**	**130**	**48**	**-**	**78**
7[b]	$Pd[OAc]_2$	3	AgOAc [2.2 equiv]	neat	130	48	-	46
8[b]	$Pd[OAc]_2$	1	AgOAc [2.2 equiv]	neat	130	48	18	8
9[b]	$Pd[OAc]_2$	5	AgOAc [1.0 equiv]	neat	130	48	38	37
10[b]	$Pd[OAc]_2$	5	AgOAc [0.5 equiv]	neat	130	48	25	14
11[b, e]	$Pd[OAc]_2$	5	AgOAc [2.2 equiv]	neat	130	48	15	67
12[b]	$Pd[OAc]_2$	5	AgOAc [2.2 equiv]	neat	130	24	13	72
13[b]	$Pd[OAc]_2$	5	AgOAc [2.2 equiv]	neat	130	12	8	70
14[b]	$Pd[OAc]_2$	5	AgOAc [2.2 equiv]	neat	60	48	23	59
15[b, c]	$Pd[OAc]_2$	5	AgOAc [2.2 equiv]	neat	130	48	-	-
16[b, d]	$Pd[OAc]_2$	5	AgOAc [2.2 equiv]	neat	130	48	-	-

[a] Reaction was done in RB under a nitrogen atm. [b] Reaction was done in a sealed tube purged with a nitrogen atm. [c] The [-] hyphen symbol refers to **6a**-(DL) not obtained.

The Pd(II)-catalyzed C(2)-H arylation of tyrosine derivative **4a**-(DL) by using 4-bromoanisole and 4-chloroanisole as the coupling partners. These reactions did not yield either **7a**-(DL) or **6a**-(DL) (Scheme 3a). Next, the C(2)-H arylation of tyrosine was attempted using different directing groups. The Pd(II)-catalyzed C(2)-H arylation of tyrosine substrate **4e**-(DL) possessing the pyrazine-2-carboxamide DG[19f] yielded the mono C(2)-H arylated product **7aa**-(DL) in 27% yield (Scheme 3a). Though the substrate **4e**-(DL) selectively gave the mono arylated product **7aa**-(DL) in low yield. The C(2)-H arylation of tyrosine substrate **4f**-(DL) possessing the quinoline-2-carboxamide DG[21a] yielded the bis C(2)-H arylated product **7ab**-(DL) in low yield (<10%, Scheme 3a). Then, we performed the C(2)-H arylation of tyrosine substrate **4g**-(DL) possessing the 5-methylisoxazole-3-carboxamide DG[18e,21b] with **5a**. This reaction afforded the bis C(2)-H arylated tyrosine derivative **7ac**-(DL) in good yield (80%, Scheme 3). The performance of the MICA DG is comparable to the picolinamide DG.[18a] The Pd(II)-catalyzed C(2)-H arylation of tyrosine substrate **4h**-(DL) possessing the simple amide DG did not yield the expected product **7ad**-(DL) (Scheme 3a). This reaction indicated the

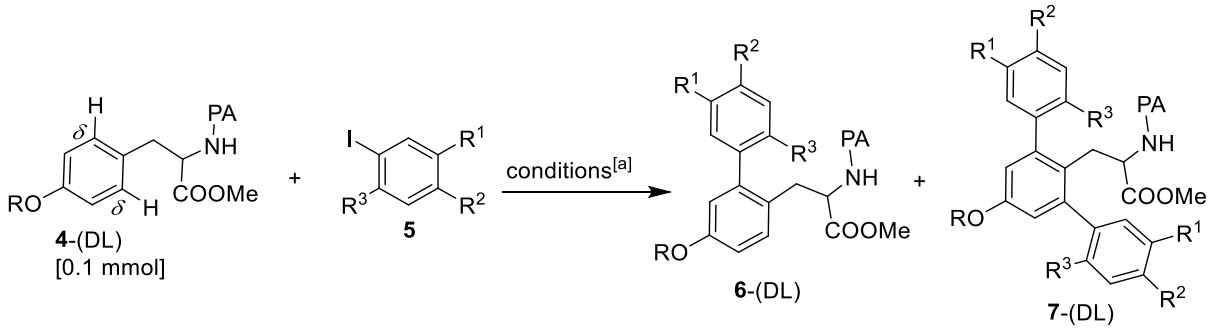


Scheme 3a: Screening of reaction condition for C(2) arylation of tyrosine using aryl halides and directing groups.

requirement for chelation assistance by bidentate DG (e.g., picolinamide or MICA). Though we obtained a comparable yield of C(2)-H arylated product using the MICA or picolinamide DG, we used picolinamide DG for further reactions as the precursor of MICA DG, 5-methylisoxazole-3-carboxylic acid is relatively expensive.

The C(2)-H arylation of tyrosine substrate **4a′**-(DL)[3j] possessing free OH group and OAc protected substrate **4j**-(DL) [14e] were not fruitful (Scheme 3b). Then, we aimed to perform additional experiments to find out the suitable condition for obtaining the mono C(2)-H arylated product **6**-(DL) using picolinamide DG. The C(2)-H arylation of **4a**-(DL) with aryl iodides **5q,r** containing electron withdrawing group (e.g., NO_2, Ac) at the *para* position and *ortho-substituted* aryl iodide **5s** were not fruitful (Scheme 3b).

Then, the C(2)-H arylation of **4a**-(DL) with aryl iodides **5i**/**5f** was attempted using only 1 equiv of AgOAc instead of 2.2 equiv. These reactions gave the inseparable mixture of products, respectively. Similarly, the C(2)-H arylation of **4a**-(DL) was attempted using 1 equiv of aryl iodides **5i**/**5f** instead of 5 equiv. The expected mono or bis arylated products **6i**-(DL)/**7i**-(DL) were not obtained using 1 equiv of **5i**. On the other hand, only the bis C(2)-H arylated product **7f**-(DL) was observed (in 23% yield) using 1 equiv of **5f** and the corresponding mono C(2)-H arylated product **6f**-(DL) was not obtained in characterizable amounts (Scheme 3b). Thus, except the result obtained using substrate **4e**-(DL), other attempts to selectively obtain the mono (*ortho*) C(2)-H arylated product (DL) were not completely successful using picolinamide DG and in all the trials we obtained the bis C(2)-H arylated product along with mono (*ortho*) C(2)-H arylated product (Table 1 and Scheme 3b).

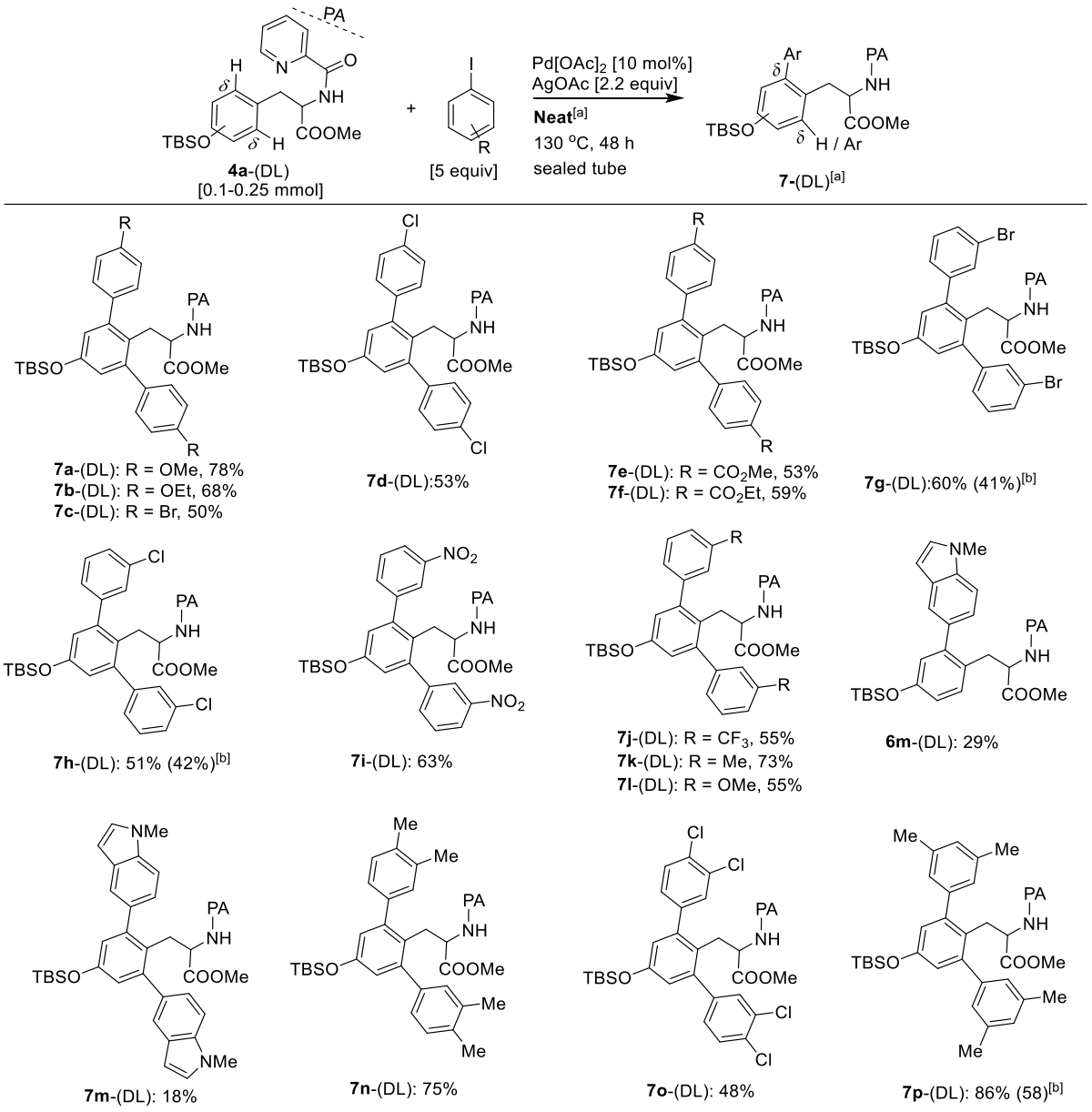


	R		R^1	R^2	R^3	
4a'-(DL)	H	**5a**	H	OMe	H	**6ae**-(DL) / **7ae**-(DL): not obtained
4a'-(DL)	H	**5i**	NO_2	H	H	**6af**-(DL) / **7af**-(DL): not obtained
4j-(DL)	Ac	**5a**	H	OMe	H	**6ag**-(DL) / **7ag**-(DL): mixture with **4j**-(DL)
4j-(DL)	Ac	**5f**	H	COOEt	H	**6ah**-(DL) / **7ah**-(DL): traces
4a-(DL)	TBS	**5q**	H	NO_2	H	**6ai**-(DL) / **7ai**-(DL): not obtained[b]
4a-(DL)	TBS	**5r**	H	Ac	H	**6aj**-(DL) / **7aj**-(DL): not obtained/traces
4a-(DL)	TBS	**5s**	H	H	COOMe	**6ak**-(DL) / **7ak**-(DL): not obtained
4a-(DL)	TBS	**5i**	NO_2	H	H	**6i**-(DL) / **7i**-(DL): mixutre[c]
4a-(DL)	TBS	**5i**	NO_2	H	H	**6i**-(DL) / **7i**-(DL): traces[d]
4a-(DL)	TBS	**5f**	H	COOEt	H	**6f**-(DL) / **7f**-(DL): mixture[e]
4a-(DL)	TBS	**5f**	H	COOEt	H	**6f**-(DL): 0%, **7f**-(DL): 23%[f]

Scheme 3b: [a] Reactions were done using conditions: aryl iodide [5 equiv], $Pd[OAc]_2$ [10 mol%], AgOAc [2.2 equiv], neat, 130 ºC, 48 h, sealed tube [purged with N_2]. [b] The reaction involving aryl iodide **5q** was done in toluene [1 mL] as the neat reaction was sluggish, and **5q** has a high mp. [c] The reaction was done using 1 equiv of AgOAc, and in this reaction, an inseparable mixture of **6i**-(DL) and **7i**-(DL) was formed. [d] The reaction was done using 1 equiv of aryl iodide **5i**. [e] The reaction was done using 1 equiv of AgOAc, and in this reaction, an inseparable mixture of **6f**-(DL) and **7f**-(DL) was formed. [f] The reaction was done using 1 equiv of aryl iodide **5f**.

We then intended to expand the substrate scope and generality of this work and assemble a library of C(2) arylated tyrosines (terphenyl-based tyrosines). The substrate **4a**-(DL) was subjected to the remote *δ*-C(sp^2)-H (*ortho*) arylation with various aryl iodides possessing a substituent at the *para* or *meta* position (e.g., OMe, OEt, Br, Cl, COOMe, COOEt, NO_2, CF_3 and Me) and disubstituted aryl iodides in neat condition. These reactions gave the corresponding bis C(2) arylated tyrosine derivatives **7a-l**-(DL) and **7n-p**-(DL) in 48-86% yields (Scheme 4). The C(2)-H arylation of **4a**-(DL) with 5-iodo-1-methylindole afforded the bis C(2) arylated tyrosine **7m**-(DL) (18%) and the mono C(2) arylated tyrosine **6m**-(DL) (29%). This reaction indicated that specifically the C(2)-H arylation of **4a**-(DL) with 5-iodo-1-methylindole might be slow. Thus, a considerable amount of **6m**-(DL) was obtained when

compared to other reactions in which the bis (*ortho*) C(2) arylated tyrosines **7a-l**-(DL) and **7n-p**-(DL) were obtained as the major products.

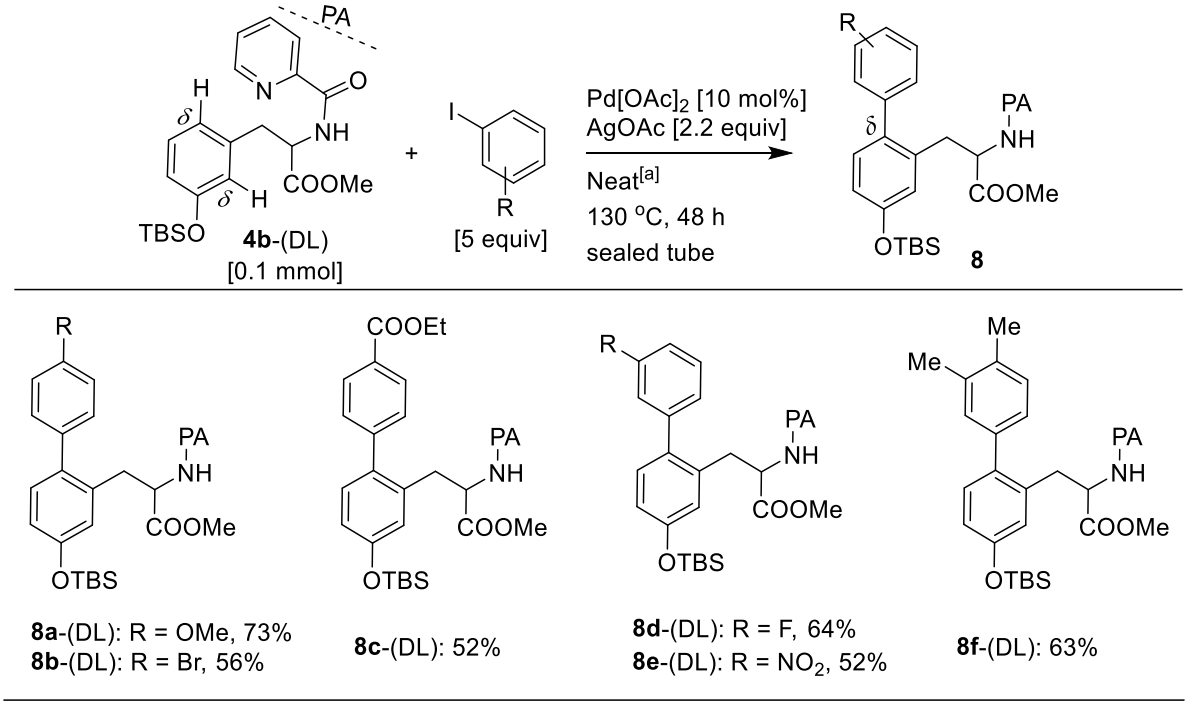


[a] Reactions done in a sealed/pressure tube purged with a nitrogen atm. [b] Reactions conditions: 4a-(DL) (0.1 mmol), ArI (4 equiv), $Pd(OAc)_2$ (10 mol%), AgOAc (2.2 equiv), 130 °C, 48 h, toluene [1 mL] in RB flask under a nitrogen atm.

Scheme 4. Construction of C(2) arylated unnatural tyrosines **7a-p**-(DL). [a] Reactions done in a sealed/pressure tube purged with a nitrogen atm. [b] Reactions conditions: **4a**-(DL) [0.1 mmol], ArI [4 equiv], $Pd[OAc]_2$ [10 mol%], AgOAc [2.2 equiv], 130 °C, 48 h, toluene [1 mL] in RB flask under a nitrogen atm.

Subsequently, an OTBS-protected *meta* tyrosine substrate **4b**-(DL) was subjected to the C(2)-H arylation with various aryl iodides in neat condition (Scheme 5). These reactions gave the

corresponding mono C(2) arylated tyrosines **8a-f**-(DL) (biaryl-based tyrosines) in 52-73% yields (Scheme 5). Due to a steric hindrance by the OTBS substituent at the *meta*-position in **4b**-(DL), the C(2)-H arylation yielded only the mono arylated products **8a-f**-(DL). This is a commonly observed trend in aromatic compounds possessing a substituent at the *meta*-position.[2,11b,18a,21c]

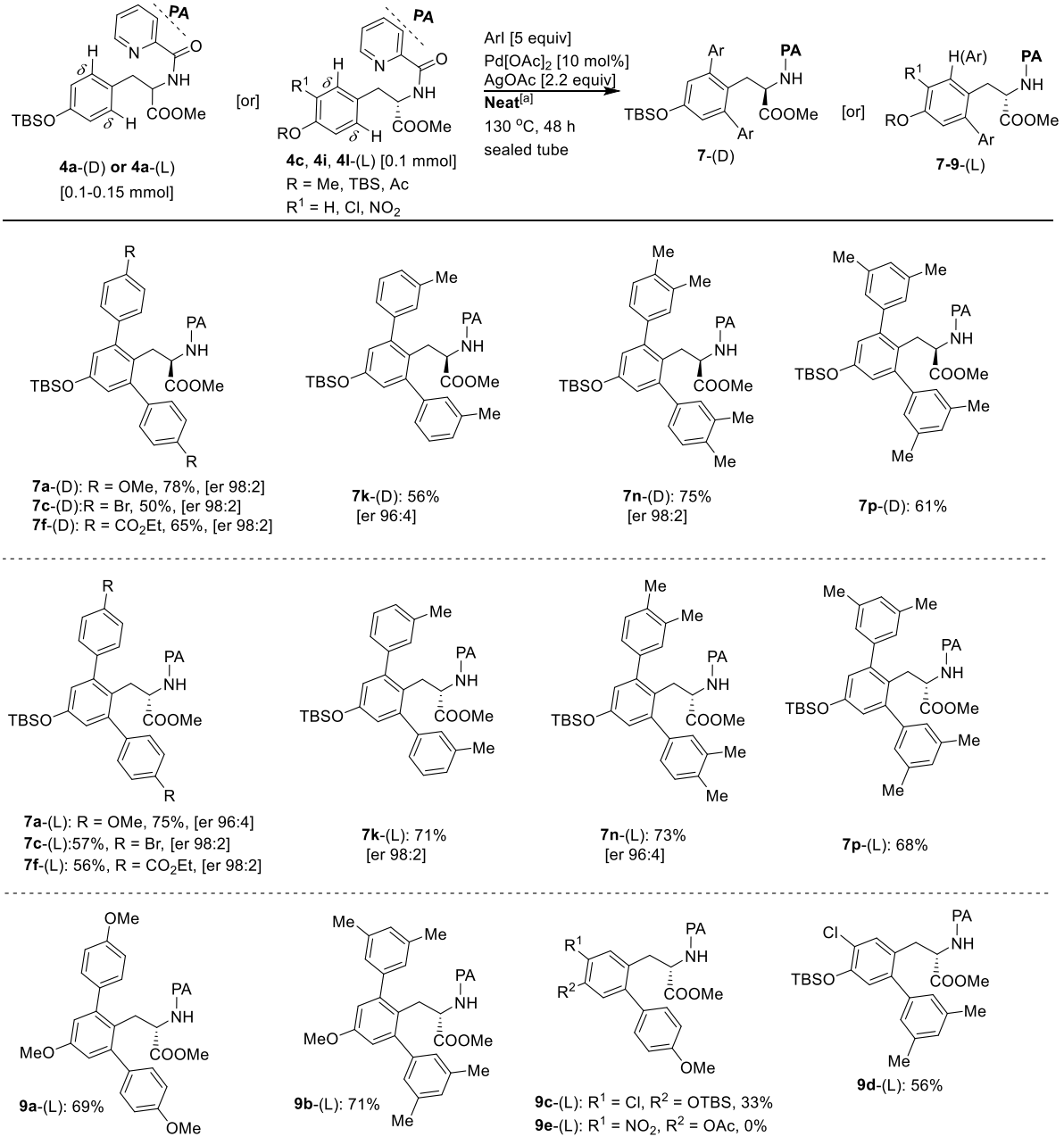


Scheme 5. Construction of C(2) arylated unnatural tyrosines **8a-f**-(DL). [a] Reaction was done in a sealed tube purged with N_2 atm.

To expand the library of enantiopure unnatural tyrosines, we continued to perform the remote *δ*-C(sp^2)-H arylation of enantiopure tyrosine substrates **4a**-(D), **4a**-(L), **4c**-(L), **4d**-(L) and **4i**-(L). At first, the enantiopure tyrosine substrate **4a**-(D) was subjected to the C(2)-H arylation with various aryl iodides possessing a substituent at the *para* or *meta* position (e.g., OMe, Br, COOEt, and Me) and disubstituted aryl iodides in neat condition. These reactions gave the corresponding bis C(2) arylated enantiopure tyrosine derivatives **7a,c,f,k,n,p**-(D) in 50-78% yields (*er* up to 98:2, Scheme 6).

Similarly, the enantiopure tyrosine substrate **4a**-(L) was subjected to the C(2)-H arylation with various aryl iodides. These reactions gave the corresponding bis C(2)-H arylated enantiopure tyrosine derivatives **7a,c,f,k,n,p**-(L) in 56-75% yields (*er* up to 98:2, Scheme 6). Then, the *δ*-C(sp^2)-H arylation of substrate **4i**-(L) with aryl iodides gave the corresponding bis C(2)-H arylated enantiopure tyrosine derivatives **9a,b**-(L) in 69-71% yields (Scheme 6). Additionally,

the δ-C(sp^2)-H arylation of *meta*-chloro tyrosine substrate **4d**-(L) with aryl iodides gave the corresponding mono C(2)-H arylated enantiopure tyrosine derivatives **9c,d**-(L) in 33-56% yields (Scheme 6).



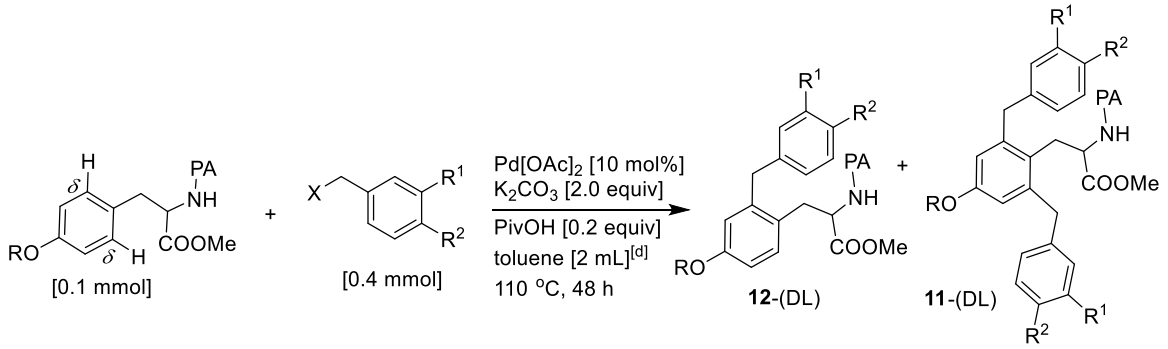
Scheme 6. Construction of C(2) arylated enantiopure unnatural tyrosines. [a] Reactions were done in a sealed tube purged with a nitrogen atm. [b] **7a,c,f,k,n,p**-(L), from **4a**-(L); **7a,c,f,k,n,p**-(D), from **4a**-(D); **9a**-(L), **9b**-(L) from **4i**-(L); **9c**-(L), **9d**-(L) from **4d**-(L); **9e**-(L) from **4c**-(L). (Scheme 6).

The δ-C(sp^2)-H arylation of enantiopure *meta*-nitro tyrosine substrate **4c**-(L) with **5a** did not yield the expected mono C(2)-H arylated enantiopure tyrosine derivative **9e**-(L). It may be

noted that substrate **4j**-(DL) without the NO_2 group also did not provide the expected arylated product (Scheme 3). At this stage, it is not clear why the substrate **4c**-(L) did not give the arylated product and we believe that the reaction might be sluggish due to both the OAc and NO_2 substituents in **4c**-(L) in neat condition and also the OAc and NO_2 substituents might not tolerating the experimental conditions.

Next, we attempted the Pd(II)-catalyzed C(2)-H benzylation of tyrosine substrate **4a**-(DL) with benzyl bromides to obtain the tyrosine-based diarylmethane scaffolds. Accordingly, the C(2)-H benzylation of **4a**-(DL) was attempted using the *ortho* C-H benzylation conditions (reported by Daugulis, Jiang and used by us earlier).[17,18a,d] Initially, we performed a few reactions to find suitable conditions for obtaining the C(2) benzylated tyrosine by using a substrate **4**-(DL), benzyl bromide (4 equiv) in the presence of the $Pd(OAc)_2$ catalyst and K_2CO_3 and PivOH additives in toluene at 110 ^oC. The C(2)-H benzylation of tyrosine substrate **4a′**-(DL) possessing free OH group using benzyl bromides **10e,h** having a substituent at the *para* or *meta* position (e.g., Cl, NO_2) were not fruitful (Scheme 7a).

Treatment of OTBS-protected substrate **4a**-(DL) with benzyl chloride (**10a′**) in the presence of the $Pd(OAc)_2$ catalyst and K_2CO_3 and PivOH additives in toluene at 110 ^oC yielded the bis C(2) benzylated tyrosine derivative **11a**-(DL) in 22% yield and the mono C(2) benzylated product **12a**-(DL) was not obtained. Next, we performed the Pd(II)-catalyzed C(2)-H benzylation of **4a**-(DL) using other benzylation reagents including benzyl acetate (**10b′**) or benzyl benzoate (**10c′**) or dibenzyl carbonate (**10d′**). These attempts did not yield the expected C(2) benzylated tyrosine derivative **11a**-(DL) (Scheme 7a).



	R		R^1	R^2	X	
4a'-(DL)	H	**10e**	Cl	H	Br	**12k**-(DL) / **11k**-(DL): mixture
4a'-(DL)	H	**10h**	H	NO_2	Br	**12l**-(DL) / **11l**-(DL): mixture
4a-(DL)	TBS	**10a'**	H	H	Cl	**12a**-(DL): 0% / **11a**-(DL): 22%
4a-(DL)	TBS	**10b'**	H	H	O(CO)Me	**12a**-(DL): 0% / **11a**-(DL): 0%
4a-(DL)	TBS	**10c'**	H	H	O(CO)Ph	**12a**-(DL): 0% / **11a**-(DL): 0%
4a-(DL)	TBS	**10d'**	H	H	O(CO)OBn	**12a**-(DL): 0% / **11a**-(DL): 0%
4a-(DL)	TBS	**10e**	Cl	H	Br	**12e**-(DL): 0% / **11e**-(DL): 78%
4a-(DL)	TBS	**10e**	Cl	H	Br	**12e**-(DL): 0% / **11e**-(DL): 65%[a]
4a-(DL)	TBS	**10e**	Cl	H	Br	**12e**-(DL): 0% / **11e**-(DL): 0%[b]
4a-(DL)	TBS	**10e**	Cl	H	Br	**12e**-(DL) / **11e**-(DL): mixture[c]
4a-(DL)	TBS	**10a**	H	H	Br	**12a**-(DL): 0% / **11a**-(DL): 57% [55%][f]
4a-(DL)	TBS	**10a**	H	H	Br	**12a**-(DL): 0% / **11a**-(DL): [0%][g,h]

Scheme 7a. Construction of C(2) benzylated tyrosines. [a] Without PivOH. [b] Without K_2CO_3. [c] Without PivOH and K_2CO_3 but using 2 equiv of KOPiv. [d] Reaction was done in a sealed tube [purged with N_2 atm]. [e] Using 1.5 equiv of 4-nitrobenzyl bromide. [f] **4a**-(DL) [0.1 mmol], neat, $Pd[OAc]_2$ [10 mol%], K_2CO_3 [2.0 equiv], PivOH [0.2 equiv], 110 °C, 36 h, sealed tube purged with N_2 atm. [g] **4a**-(DL) [0.15 mmol], 1,4-dioxane, KOAc [2 equiv] at 130 °C, 24 h, RB flask under N_2 atm. [h] **4a**-(DL) [0.15 mmol], 1,4-dioxane, AgOAc [1.5 equiv] at 130 °C, 48 h, RB flask under N_2 atm.

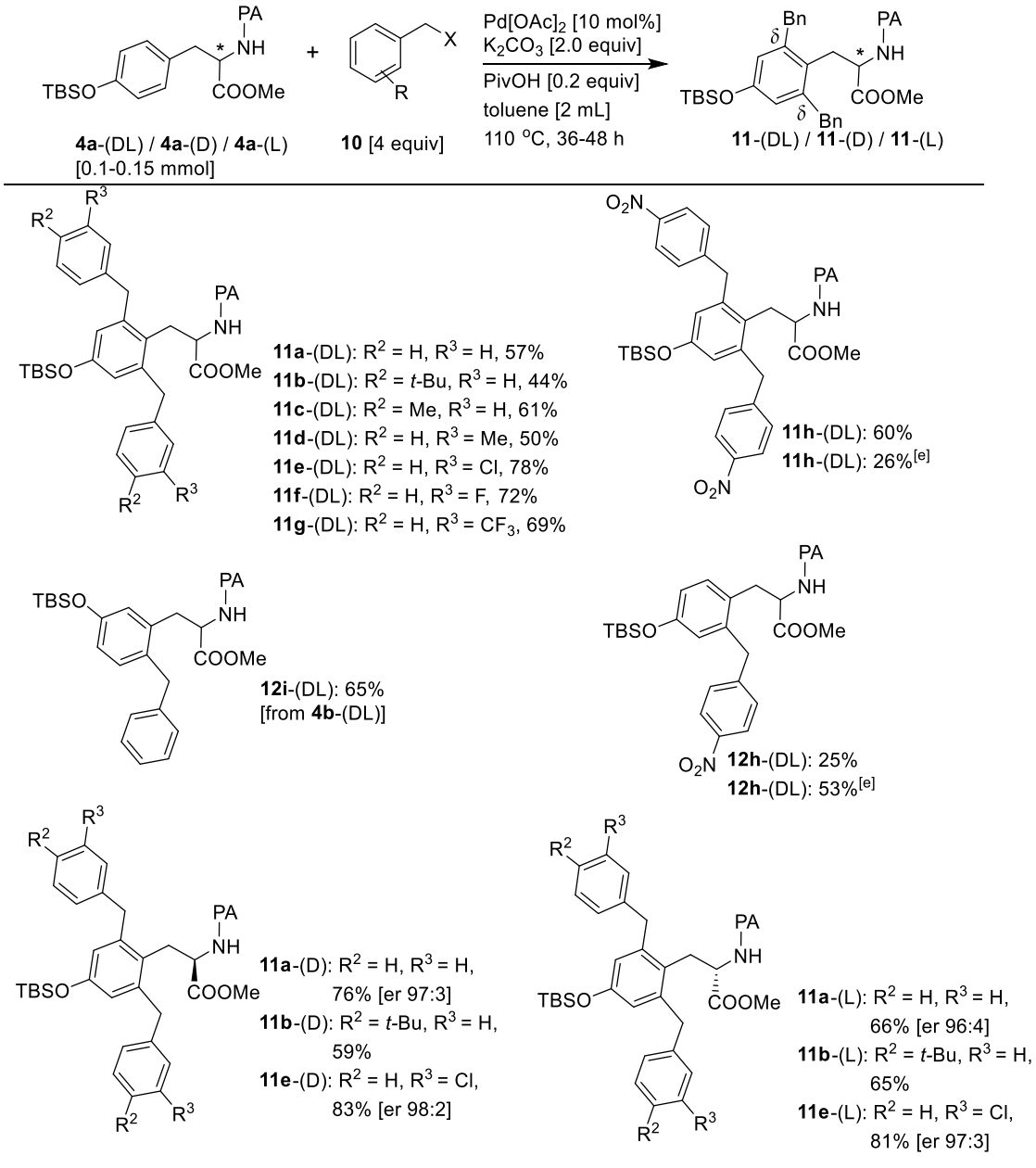
Next, we aimed to find out the role of additives, towards this, we treated substrate **4a**-(DL) with *meta*-chloro benzyl chloride (**10e**) in the presence of the $Pd(OAc)_2$ catalyst and K_2CO_3 and PivOH additives in toluene at 110 °C. This reaction yielded the bis C(2) benzylated tyrosine derivative **11e**-(DL) in 78% yield and the mono C(2) benzylated tyrosine derivative **12e**-(DL) was not obtained in characterizable amounts. The same reaction without using PivOH gave the product **11e**-(DL) in 65% yield and this reaction indicated that the use of PivOH as an additional additive seemed to help or improve the yield of the benzylation process. In general, it is known that PivOH (*viz.* pivalate anion) is proposed to act as a key component/ligand to the Pd complex in promoting the C-H functionalization process.[21d,e] Next, we treated substrate **4a**-(DL) with *meta*-chloro benzyl chloride (**10e**) in the presence of the $Pd(OAc)_2$ catalyst and PivOH and without K_2CO_3. This reaction did not provide the expected product **11e**-(DL) and

it indicated usage of an alkali metal salt is necessary and it acts as the halide ion (e.g. iodide anion) scavenger to regenerate the Pd(II) catalyst in the proposed bidentate DG-aided Pd^{II}-Pd^{IV} catalytic cycle.[2,3,17-20] Subsequently, we treated substrate **4a**-(DL) with *meta*-chloro benzyl chloride (**10e**) in the presence of the $Pd(OAc)_2$ catalyst and without PivOH and K_2CO_3 but using 2 equiv of KOPiv. While the proton NMR indicated the formation of a considerable amount of mono C(2) benzylated tyrosine derivative **12e**-(DL). However, we could not isolate **12e**-(DL) in pure form (the yield was not quantified) and it was isolated along with **4a**-(DL) due to similar R_f values of **12e**-(DL)/**4a**-(DL). This attempt indicated that the usage of PivOH (as a proton source) [2, 21d, e] and K_2CO_3 as independent additives are necessary to promote the C-H benzylation process.

Furthermore, we wished to find out whether the benzylation of **4a**-(DL) can be done in a neat condition. Towards this, initially, we treated **4a**-(DL) with benzyl bromide (**10a**) in the presence of the $Pd(OAc)_2$ catalyst and PivOH and K_2CO_3 in toluene at 110 ^oC. This reaction yielded the bis C(2) benzylated tyrosine derivative **11a**-(DL) in 57% yield (Scheme 7a). We then performed the same reaction in neat condition, which afforded **11a**-(DL) in 55% yield (Scheme 7a). Finally, we performed the Pd(II)-catalyzed C(2)-H benzylation of **4a**-(DL) with benzyl bromide using KOAc or AgOAc as additives instead of K_2CO_3 in 1,4-dioxane solvent and these attempts did not yield the product **11a**-(DL). Except for the reaction conditions which indicated the formation of **12e**-(DL), in all other reaction conditions screened, we did not get the corresponding mono C(2) benzylated tyrosine derivative in characterizable amounts (Scheme 7a).

Having done the screening of reaction conditions and for expanding the substrate scope, we then treated **4a**-(DL) with various benzyl bromides (4 equiv) in the presence of the $Pd(OAc)_2$ catalyst and K_2CO_3 and PivOH additives in toluene at 110 ^oC. These reactions yielded the corresponding bis C(2) benzylated tyrosine derivatives **11b-g**-(DL) in 44-78% yields (Scheme 7b). The C(2)-H benzylation of **4a**-(DL) with 4-nitrobenzyl bromide (4 equiv) afforded the bis C(2) benzylated tyrosine **11h**-(DL) (60%) and the mono C(2)-H benzylated tyrosine **12h**-(DL) (25%). The benzylation of **4a**-(DL) with 1.5 equiv of 4-nitrobenzyl bromide afforded the bis C(2) benzylated tyrosine **11h**-(DL) in 26% yield and mono C(2) benzylated tyrosine **12h**-(DL) in 53% yield. In this reaction, a proportionately increased amount of mono C(2) benzylated tyrosine **12h**-(DL) was obtained. These reactions indicated that specifically the C(2)-H benzylation of **4a**-(DL) with 4-nitrobenzyl bromide might be slow when compared to other benzylation reactions and thus, yielded the mono C(2) benzylated tyrosine **12h**-(DL) in

considerable amounts. Subsequently, OTBS-protected *meta* tyrosine substrate **4b**-(DL) was subjected to the C(2)-H benzylation with benzyl bromide to afford the mono C(2) benzylated tyrosine derivative **12i**-(DL) in 65% yield (Scheme 7b). The C(2) benzylation of **4b**-(DL) gave the mono C(2) benzylated tyrosine derivatives **12i**-(DL) due to a steric hindrance by the substituent at the *meta*-position in **4b**-(DL) and this observation is similar to the C(2) arylation of **4b**-(DL) which gave the mono C(2) arylated products **8a-f**-(DL). Next, we performed the C(2)-H benzylation of enantiopure tyrosine substrates **4a**-(D) and **4a**-(L) with benzyl bromides to obtain the enantiopure tyrosine-based diarylmethane scaffolds. Accordingly, various bis C(2) benzylated enantiopure tyrosine derivatives **11a,b,e**-(D) (59-83% yields, *er* up to 98:2) and **11a,b,e**-(L) (65-81% yields, *er* up to 97:3) were obtained from their corresponding substrates (Scheme 7b).



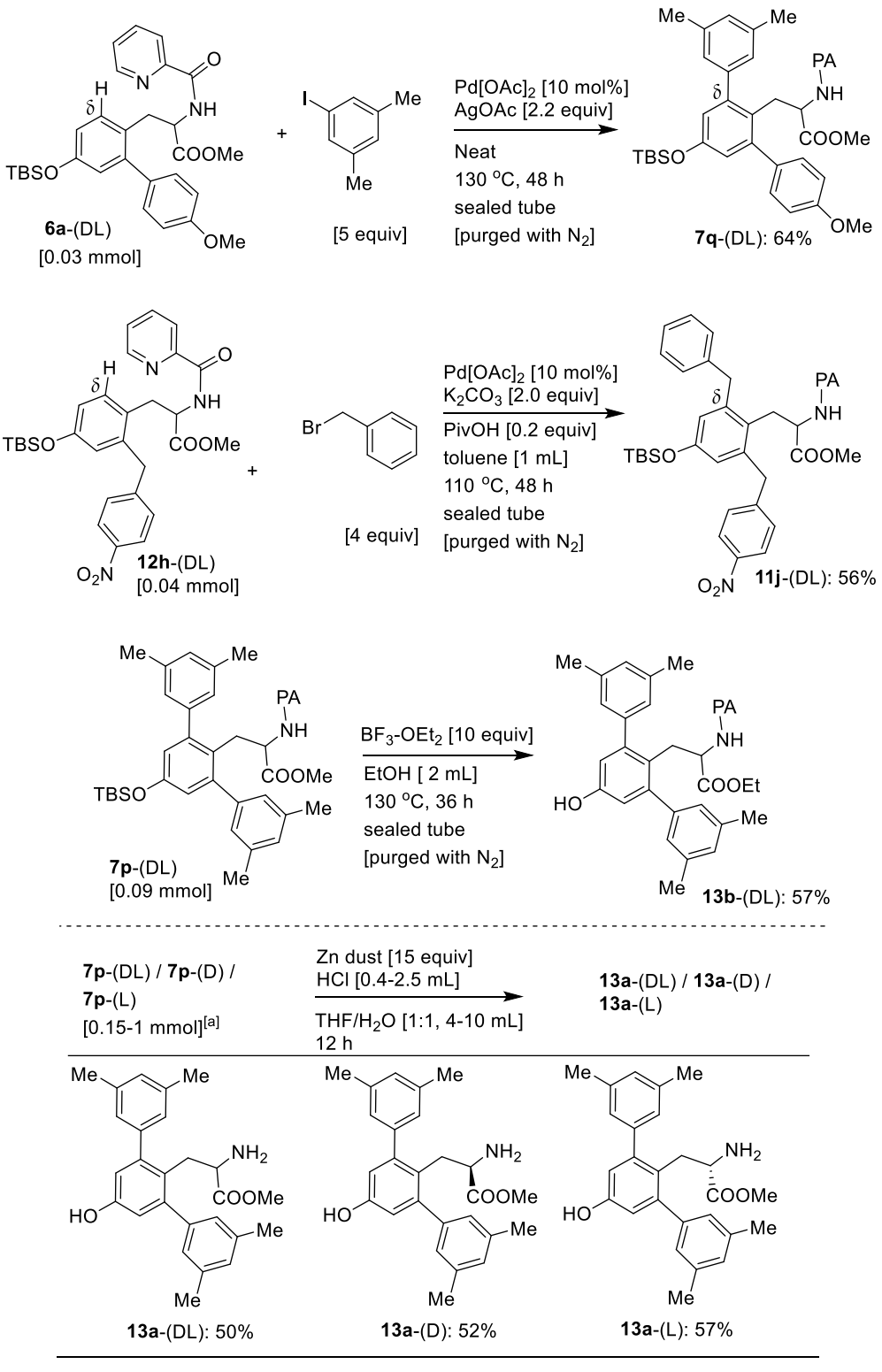
Scheme 7b: Construction of C(2) benzylated tyrosines.

Then, we wished to reveal the usefulness and synthetic utility of this protocol comprising of the Pd(II)-catalyzed, picolinamide-directed C(2)-H (*ortho*) arylation or benzylation of tyrosines. At first, we attempted the second C(2)-H arylation and benzylation reactions using the mono arylated and benzylated tyrosines **6a**-(DL) and **12h**-(DL) (Scheme 8). These reactions afforded the corresponding bis arylated tyrosine **7q**-(DL) and bis benzylated tyrosines **11j**-(DL) having different aryl or benzyl groups, respectively, at the C(2) position (Scheme 8). We then attempted the deprotection of the OTBS group in a representative bis C(2) arylated tyrosine **7p**-(DL) using $BF_3 \cdot OEt_2$ in EtOH, which yielded the bis C(2) arylated tyrosine **13b**-

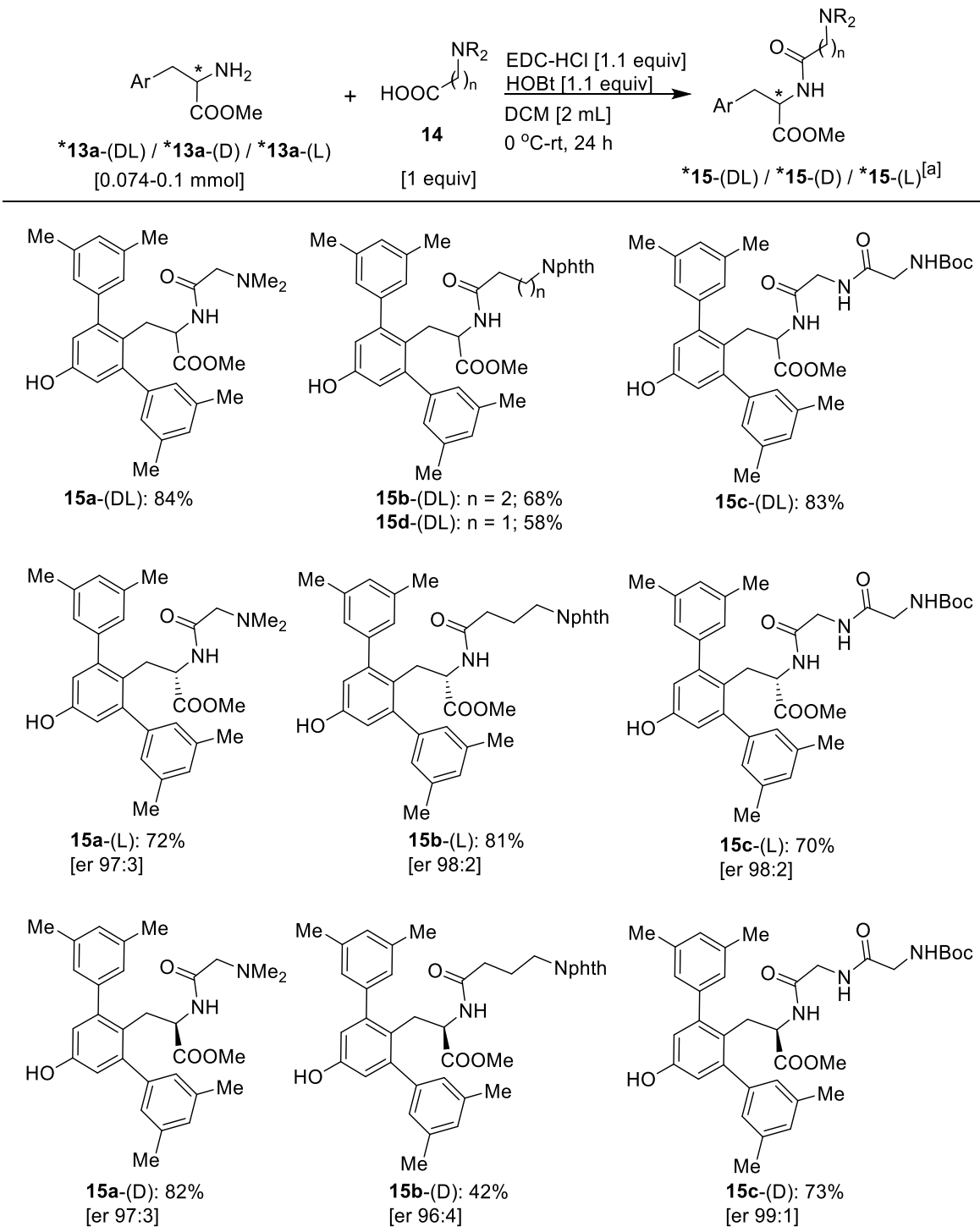
(DL) (57%) having the free phenolic group and COOEt moiety *via* the transesterification under the experimental conditions (Scheme 8).

Next, we intended to show the removal of the picolinoyl group (directing group) from the C(2) (*ortho*) arylated tyrosine motif. A few trials were made to find out the suitable reaction conditions for removing the picolinoyl group. We succeeded in removing the picolinoyl group by treating **7p**-(DL) with Zn dust and 12 N HCl in a mixture of THF/H_2O at rt for 12 h in the air.[22] This process gave the bis C(2) arylated tyrosine **13a**-(DL) having the free NH_2 and TBS moiety deprotected phenolic groups. Following a similar procedure, bis C(2) arylated enantiopure tyrosines **13a**-(D) and **13a**-(L) having the free NH_2 and TBS moiety deprotected phenolic groups were obtained from their corresponding substrates **7p**-(D) and **7p**-(L) (Scheme 8).

Finally, we attempted assembling some peptides using bis C(2) arylated tyrosine **13a**-(DL) and enantiopure bis C(2) arylated tyrosines **13a**-(D) and **13a**-(L) (Scheme 9). Initially, bis C(2) arylated tyrosine **13a**-(DL) was subjected to the amide coupling reaction with *N,N*-dimethylglycine or *N*-phthaloyl *β*-alanine or *N*-phthaloyl GABA or Boc-Gly-Gly-OH. These trials afforded the corresponding bis C(2) arylated tyrosine-based peptides **15a-d**-(DL) in 58-84% yields (Scheme 9). Similarly, the bis C(2) arylated enantiopure tyrosines **13a**-(L) and **13a**-(D) were subjected to the amide coupling reaction with *N,N*-dimethylglycine or *N*-phthaloyl GABA or Boc-Gly-Gly-OH. These trials afforded the corresponding enantiopure bis C(2) arylated tyrosine-based peptides **15a-c**-(L) and **15a-c**-(D) in 42-82% yields (*er* up to 99:1) (Scheme 9).



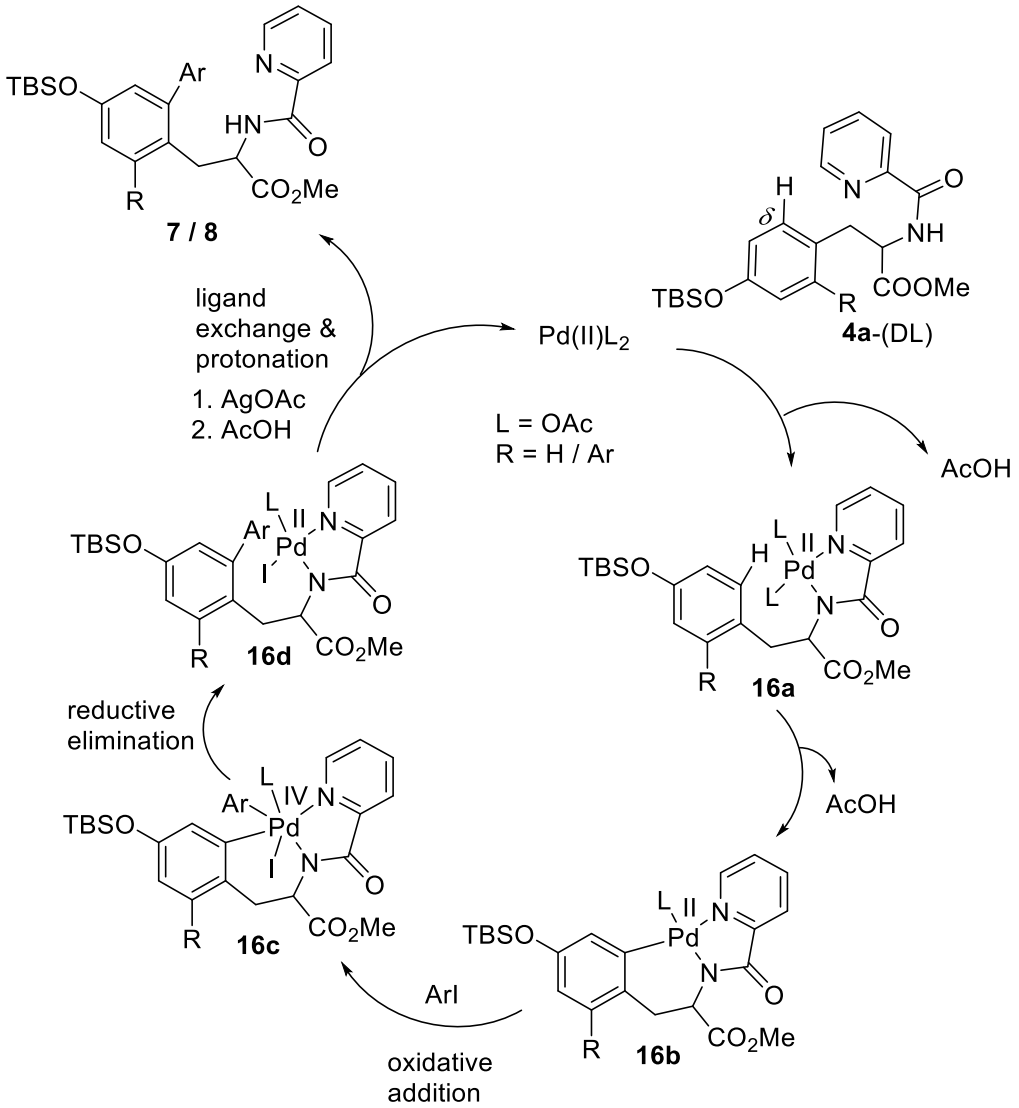
Scheme 8. Examples of second arylation/benzylation of **6a**-(DL) and **12h**-(DL) and the deprotection of TBS and picolinoyl groups. [a] **7p**-(DL) [0.15 mmol, THF/H_2O [4 mL]. **7p**-(D) [1 mmol, THF/H_2O [10 mL]. **7p**-(L) [0.4 mmol, THF/H_2O [6 mL].



Scheme 9. Construction of C(2)-H arylated tyrosine-based peptides. [a] The compounds ***15**-(DL) / ***15**-(D) / ***15**-(L) were obtained from their corresponding substrates ***13a**-(DL) / ***13a**-(D) / ***13a**-(L) and amino acid/peptide substrates **14**.

In general, the bidentate DG picolinamide-directed C–H activation and functionalization of organic molecules is proposed to undergo *via* a Pd(II)/Pd(IV) redox cycle mechanism.[2,3,16-20] In concurrence with the proposed mechanism of the bidentate DG-assisted C–H

functionalization reaction, a plausible mechanism for the picolinamide DG-assisted Pd(II)-catalyzed arylation of the δ-C(sp^2)-H bond of tyrosine substrate **4a**-(DL) is proposed (Scheme 10). The coordination of the picolinamide DG unit in **4a**-(DL) to the Pd(II) metal center is followed by concerted metalation deprotonation (CMD), generating the plausible six-membered Pd(II) species **16b**. Oxidative addition of the Pd(II) species **16b** with an aryl iodide then forms the Pd(IV) species **16c**. Then intermediate **16c** undergoes reductive elimination to generate the new C–C bond in **16d**. Halide abstraction by a halide ion scavenger (e.g., AgOAc) followed by the protonolysis of the intermediate **16d** affords the δ-C(2)-H arylated product **7**/**8** and the active Pd(II) species is regenerated in the catalytic cycle (Scheme 10).



Scheme 10: Plausible mechanism in concurrence with the literature.[2,3,16-20] Pd(II)-catalyzed picolinamide DG-aided δ-C(2)-H functionalization (arylation) tyrosine substrate **4a**-(DL).

We have performed the HPLC analyses to obtain the HPLC patterns of the substrates used, C(2) arylated and benzylated enantiopure tyrosine compounds (see the supporting information). Substrates **4a**-(DL), **4a**-(D) and **4a**-(L) were prepared from the corresponding commercially available DL-, D-, and L-tyrosines. Enantiopurity of substrates **4a**-(D) (*er* 99:1), **4a**-(L) (*er* 98:2) were ascertained from the HPLC and polarimeter analysis data. Then, the HPLC profile of the enantiopure products **7a,c,f,k,n**-(D), **7a,c,f,k,n**-(L), **11a,e**-(D), **11a,e**-(L) and their corresponding racemic compounds **7a,c,f,k,n**-(DL) and **11a,e**-(DL) were ascertained. For the enantiopure products **7p**-(D), **7p**-(L), **11b**-(D), and **11b**-(L), the HPLC analysis profiles could not be ascertained under different columns and methods. Based on the optical rotation data and in analogy to the other products (Schemes 6 and 7) these compounds are believed to be enantiopure.

Substrate **4c**-(L) was prepared from commercially available 3-nitro-L-tyrosine ethyl ester hydrochloride. Substrate **4d**-(L) was prepared from commercially available 3-chloro-L-tyrosine and substrate **4i**-(L) was prepared from commercially available *O*-methyl-L-tyrosine. The substrates **4c**-(L), **4d**-(L), and **4i**-(L) were prepared using the method used to assemble **4a**-(L). Substrates **4c**-(L), **4d**-(L), and **4i**-(L) were presumed to be enantiopure based on their HPLC and polarimeter analysis data (the corresponding **4c**-(DL), **4d**-(DL), and **4i**-(DL) were not prepared (as their corresponding starting materials are not commercially available).

Accordingly, for the enantiopure products **9a-d**-(L), the HPLC profiles were obtained but their corresponding racemic products were not synthesized. Based on the optical rotation data, in analogy to the other products (Scheme 6) and the available HPLC profiles of the products **9a-d**-(L), these compounds are believed to be enantiopure. Furthermore, the HPLC profiles of the enantiopure peptides **15a-c**-(D), **15a-c**-(L) and their corresponding racemic compounds **15a-c**-(DL) were ascertained. The HPLC profiles of the racemic/enantiopure compounds **13a**-(DL), **13a**-(D) and **13a**-(L) could not be ascertained using different chiral columns and methods. Given the compounds **13a**-(D) and **13a**-(L) were used as the starting materials for obtaining the compounds **15a-c**-(D) and **15a-c**-(L) whose HPLC profiles were obtained; thus, indirectly, the compounds **13a**-(D) and **13a**-(L) are believed to be enantiopure based on their optical rotation data and the enantiopurity compounds **15a-c**-(D) and **15a-c**-(L). Based on the observed results of arylation and benzylation of enantiopure tyrosine substrates **4a**-(D) and **4a**-(L), it is believed that the racemization is minimum at the chiral centers of these substrates under the experimental conditions.

Conclusion:

In summary, we have shown the application of the Pd(II)-catalyzed picolinamide-directed site-selective δ-C(sp^2)-H arylation and benzylation of C(2) position of the aryl ring in tyrosine derivatives and expansion of the library of unnatural tyrosines. Various racemic and enantiopure bis C(2) arylated and benzylated unnatural tyrosine derivatives were assembled in good yields. Considering the importance of tyrosine derivatives, and biaryl amino acid derivatives, this work is a contribution to the expansion of substrate scope in site-selective remote δ-C-H functionalization reaction and its application in the synthesis of unnatural arylated amino acid derivatives including biaryl- or terphenyl-based[5,6,23] and diarylmethane-based[24] tyrosine scaffolds.

General. All reactions were done in an oven-dried round-bottom flask or sealed/pressure tube in anhydrous solvents or neat condition under nitrogen atm. TLC analyses were performed on silica gel or silica gel 60 F_{254} pre-coated plates and components were visualized with exposure to iodine vapour or by IR radiation under a UV lamp. The column chromatography purification was performed on silica gel (100-200 mesh) or neutral alumina (eluent = ethyl acetate:hexanes). ^{1}H NMR and ^{13}C{^{1}H} NMR spectra of samples were recorded on a 400 and ~101 MHz spectrometer (using TMS as an internal standard). The HRMS data were obtained from the QTOF mass analyzer using the electrospray ionization (ESI) method. The IR spectra of samples have been recorded either using KBr pellets or in an appropriate solvent. For finding the specific rotations of enantiopure samples, the solutions were prepared in $CHCl_3$ solvent, polarimeter data were recorded at 589 nm wavelength using 100 mm cell length, concentration (c) taken as g/100 mL. The HPLC analysis was carried out on isolated samples. Isolated yields were given, and yields were not optimized. Sometimes there is variation in yields and enantiomeric ratio for the corresponding racemic/enantiopure pairs, this is perhaps based on the collection of pure fractions from the column chromatography based on the TLC and also may be due to inadvertent handling/processing errors of samples. Substrate **4a′**-(DL) (K. Li, G. Tan, J. Huang, F. Song, J. You, *Angew. Chem. Int. Ed.* **2013**, *52*, 12942-12945) and **4j**-(DL) (L. Lukasevics, A. Cizikovs, L. Grigorjeva, *Org. Lett.* **2021**, *23*, 2748-2753) are known compounds, and almost pure crude samples prepared and used as such in the next step. Substrate **4a**-(L) (X. Wang, S. Niu, L. Xu, C. Zhang, L. Meng, X. Zhang, D. Ma, *Org. Lett.* **2017**, *19*, 246-249) is a known compound, we prepared it by using the known procedure, and characterized by NMR/Mass analysis and used in this study. The chiral version of samples **4e**-

(L) and **4f**-(L) were used by Ma *et al.* (X. Wang, S. Niu, L. Xu, C. Zhang, L. Meng, X. Zhang, D. Ma, *Org. Lett.* **2017**, *19*, 246-249). However, we have prepared, characterized, and used the racemic version of samples **4e**-(DL) and **4f**-(DL).

A typical procedure for the esterification of tyrosine (Procedure A):

An appropriate amount of tyrosine (1-10 mmol) was dissolved in dry MeOH (2-20 mL) followed by the addition of thionyl chloride (1 equiv) at 0 ^{o}C in a nitrogen atm and the resulting reaction mixture was stirred overnight at 60 ^{o}C in a round bottom flask fitted with a condenser with calcium chloride guard tube on it. Then, the resulting solution was concentrated in a vacuum to give the corresponding tyrosine methyl ester hydrochloride salt which was further used in the next step as such.

A typical procedure for *O*-silylation of tyrosine ester (Procedure B): To a solution of tyrosine methyl ester hydrochloride salt obtained from Procedure A (1-10 mmol) in DCM (2-20 mL), imidazole (2 equiv), DMAP (0.1 equiv) and TBSCl (1.2 equiv) were added, and the resulting solution was stirred at rt for 48 h under a nitrogen atmosphere. Then, the solution was quenched with saturated $NaHCO_3$ solution. The organic layers were washed with $NaHCO_3$ and brine solution, and evaporated, then the resulting crude corresponding *O*-TBS protected, tyrosine derivative, was then used as such for the next step.

A typical procedure for the preparation of *O*-TBS protected tyrosine ester linked with directing group (Procedure C): An appropriate amount of (directing group) carboxylic acid (1-10 mmol), 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide (1.1 equiv), 1-hydroxybenzotriazole hydrate (1.1 equiv) in DCM (2-20 mL) were stirred for 1 h at 0 ^{o}C under a nitrogen atm. Next, an appropriate amount of *O*-TBS protected tyrosine methyl ester (1 equiv) (1 equiv) was added to the above mixture and stirred at rt for 24 h. Then, the resulting solution was subjected to an aq. workup and washed with aq. sodium bicarbonate solution. Then, the resulting crude reaction mixture was purified on silica gel column chromatography (eluent = EtOAc:hexanes) to obtain corresponding *O*-TBS protected tyrosine ester linked with directing group (this procedure was reported by Ma et al (X. Wang, S. Niu, L. Xu, C. Zhang, L. Meng, X. Zhang, D. Ma, *Org. Lett.* 2017, *19*, 246-249) (a similar procedure used to prepare the peptide molecules from the corresponding picolinoyl group removed tyrosine derivative (obtained from procedure G) possessing the free phenolic OH and amino groups).

General procedure for the Pd(II)-catalyzed, directing group-aided ortho C-H arylation of *O*-TBS protected tyrosine ester linked with directing group.(Procedure D): A mixture of an appropriate tyrosine carboxamide possessing a directing group (0.1-0.15 mmol, 1 equiv), an appropriate aryl iodide (5 equiv), $Pd(OAc)_2$ (10 mol%) and AgOAc (2.2 equiv) was added

in a sealed/pressure tube capped with silicone septum/Teflon which was heated under the neat condition at 130 ^{o}C for 48 h (the tube was purged with a nitrogen atm). After the reaction period, purification of the reaction mixture by column chromatography on silica gel (eluent = EtOAc:hexanes) gave the corresponding ortho C-H arylated tyrosine carboxamide.

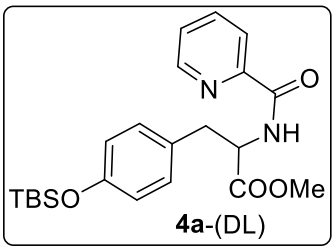
General procedure for the Pd(II)-catalyzed, directing group-aided ortho C-H benzylation of *O*-TBS protected tyrosine ester linked with directing group (procedure E): A mixture of an appropriate tyrosine carboxamide possessing the picolinamide DG (0.1-15 mmol, 1 equiv), an appropriate benzyl bromide (4 equiv), $Pd(OAc)_2$ (10 mol%), K_2CO_3 (2 equiv) and PivOH (0.2 equiv) in anhydrous toluene (1-2 mL) was heated in a sealed tube capped with Teflon cap at 110 ^{o}C for 48 h (the tube was purged with 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 silica gel (eluent = EtOAc:hexanes) gave the corresponding ortho C-H benzylated tyrosine carboxamide.

A typical procedure for the deprotection of *O*-TBS group and transesterification of ortho C-H arylated tyrosine (procedure F): To a mixture of an appropriate ortho C-H arylated tyrosine (0.09 mmol), $BF_3.OEt_2$ (10 equiv), EtOH (2 mL) were added in a sealed tube (the tube was purged with a nitrogen atm) and the reaction mixture was heated for 36 h at 110 ^{o}C. After completion, the reaction mixture was quenched with saturated $NaHCO_3$ solution and extracted with ethyl acetate. Th organic layers were dried with anhydrous Na_2SO_4 and concentrated in a vacuum, which was then further purified on silica gel column chromatography (eluent = EtOAc:hexanes) to give the corresponding product.

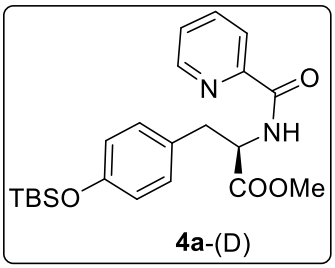
A typical procedure for the removal of the picolinoyl group after C-H arylation (procedure G): To an appropriate ortho C-H arylated tyrosine carboxamide possessing the picolinamide DG (0.15-0.4 mmol, 1.0 equiv) dissolved in H_2O/THF (ratio = 1:1, 4-8 mL) HCl (12 N, 0.3 mL) was added, and the mixture was stirred at rt for 15 min. Zinc dust (15 equiv) was then added in three portions and the mixture was stirred at rt. After 24 h, the reaction was filtered through a celite plug. The filtrate was transferred into a separating funnel with 2 M NaOH (20-50 mL) and extracted with DCM. Then, the resulting crude reaction mixture was purified using silica gel column chromatography to obtain the corresponding picolinoyl group removed tyrosine derivative possessing the free phenolic OH and amino groups.

A typical procedure for the preparation of *O*-acetylated of 3-nitro-L-tyrosine ethyl ester linked with directing group (Procedure H): An appropriate amount of picolinic acid (1 mmol), 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide (1.1 equiv), 1- hydroxybenzotriazole hydrate (1.1 equiv) in DCM (2 mL) were stirred at 0 ^{o}C for 1 h under a nitrogen atm. Next, an

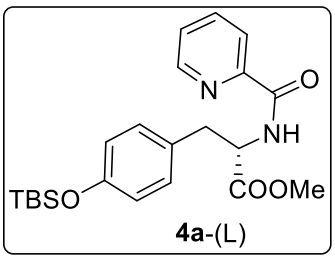
appropriate amount of 3-nitro-L-tyrosine ethyl ester hydrochloride (1 equiv) was added to the above mixture and stirred at rt for 24 h. Then, the resulting solution was subjected to an aq. workup and washed with aq. sodium bicarbonate solution and the resulting solution was evaporated. Then, the crude reaction mixture was purified on silica gel column chromatography (eluent = EtOAc:hexanes) to obtain 3-nitro-L-tyrosine ethyl ester linked with picolinamide DG (having free phenolic OH), which was further used as such in next step. Then, an appropriate amount of 3-nitro-L-tyrosine ethyl ester linked with picolinamide DG (having free phenolic OH) was dissolved in DCM (2 mL) and Et_3N (2 equiv), acetyl chloride (1.2 equiv) was sequentially added to this solution. Then the resulting reaction mixture was stirred was for 24 h under nitrogen atm and subjected to an aq. workup and washed with aq. sodium bicarbonate solution and the solution was evaporated. Then, the resulting crude reaction mixture was purified on silica gel column chromatography (eluent = EtOAc:hexanes) to obtain corresponding *O*-acetylated of 3-nitro-L-tyrosine ethyl ester linked with directing group.

Methyl 3-(4-((tert-butyldimethylsilyl)oxy)phenyl)-2-(picolinamido)propanoate (4a-(DL)): 

The compound **4a**-(DL) was obtained from procedure A, B and C after purification by column chromatography on silica gel (EtOAc:hexanes = 30:70) as a colourless solid (3.26 g, 79%, 10 mmol scale); R_f (EtOAc/hexanes = 30:70) 0.5; mp: 76-78 ^oC; IR (DCM): 3387, 2953, 1744, 1507 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ_H 8.52 (1H, d, J = 4.0 Hz), 8.47 (1H, d, J = 8.1 Hz), 8.14 (1H, d, J = 7.8 Hz), 7.80 (1H, t, J = 7.7 Hz), 7.39 (1H, t, J = 5.9 Hz), 7.04 (2H, d, J = 7.6 Hz), 6.75 (2H, d, J = 7.5 Hz), 5.04-4.99 (1H, m), 3.70 (3H, s), 3.17 (2H, d, J = 5.9 Hz), 0.96 (9H, s), 0.16 (6H, s); $^{13}C\{^1H\}$ NMR (~101 MHz, $CDCl_3$): δ_C 171.8, 163.8, 154.6, 149.2, 148.2, 137.1, 130.2, 128.6, 126.2, 122.1, 120.1, 53.4, 52.1, 37.4, 25.6, 18.1, -4.5; HRMS (ESI): *m/z* $[M+H]^+$ calcd for $C_{22}H_{31}N_2O_4Si$: 415.2053; found: 415.2035. The HPLC of compound **4a**-(DL) was determined by using the Daicel Chiralpak IC column, hexane/*i*-PrOH 95:05, flow rate 1.0 mL/min, UV detection at 254 nm, t_D = 46.14 min, t_L = 48.41 min.

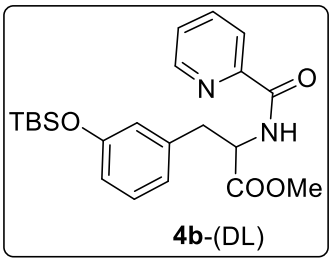
Methyl (*R*)-3-(4-((tert-butyldimethylsilyl)oxy)phenyl)-2-(picolinamido)propanoate (4a-D): 

The compound **4a**-(D) was obtained from procedure A, B and C after purification by column chromatography on silica gel (EtOAc:hexanes = 30:70) as a colourless solid (3.21 g, 77%, 10 mmol scale); R_f (EtOAc/hexanes = 30:70) 0.5; mp: 76-78 ^oC; IR (DCM): 3385, 2953, 1744, 1508 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ_H 8.54 (1H, d, J = 4.5 Hz), 8.48 (1H, d, J = 8.2 Hz), 8.15 (1H, d, J = 7.8 Hz), 7.83 (1H, t, J = 7.7 Hz), 7.42 (1H, t, J = 6.6 Hz), 7.05 (2H, d, J = 8.1 Hz), 6.76 (2H, d, J = 8.1 Hz), 5.05-5.00 (1H, m), 3.72 (3H, s), 3.18 (2H, d, J = 6.1 Hz), 0.97 (9H, s), 0.17 (6H, s); $^{13}C\{^1H\}$ NMR (~101 MHz, $CDCl_3$): δ_C 171.9, 163.9, 154.7, 149.3, 148.3, 137.2, 130.3, 128.7, 126.3, 122.2, 120.2, 53.6, 52.3, 37.5, 25.7, 18.2, -4.4; HRMS (ESI): *m/z* $[M+Na]^+$ calcd for $C_{22}H_{30}N_2NaO_4Si$: 437.1873; found: 437.1881. $[\alpha]^{25}_D$ = -38.9 (c = 0.02 g/mL, $CHCl_3$). The enantiomeric ratio (er 99:1) of compound **4a**-(D) was determined by using the Daicel Chiralpak IC column, hexane/*i*-PrOH 95:05, flow rate 1.0 mL/min, UV detection at 254 nm, t_D = 47.33 min, t_L = 50.64 min.

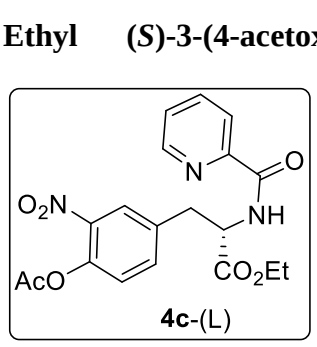
Methyl (*S*)-3-(4-((tert-butyldimethylsilyl)oxy)phenyl)-2-(picolinamido)propanoate (4a-(L)): 

The compound **4a**-(L) was obtained from procedure A, B and C after purification by column chromatography on silica gel (EtOAc:hexanes = 30:70) as a colourless solid (3.18 g, 77%, 10 mmol scale); R_f (EtOAc/hexanes = 30:70) 0.5; mp: 77-79 ^oC; IR (DCM): 3385, 2953, 1744, 1508 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ_H 8.54 (1H, d, J = 4.6 Hz), 8.47 (1H, d, J = 8.3 Hz), 8.16 (1H, d, J = 7.8 Hz), 7.84 (1H, td, J_1 = 7.7 Hz, J_2 = 1.5 Hz), 7.44-7.41 (1H, m), 7.05 (2H, d, J = 8.4 Hz), 6.76 (2H, d, J = 8.4 Hz), 5.06-5.00 (1H, m), 3.72 (3H, s), 3.18 (2H, d, J = 6.2 Hz), 0.97 (9H, s), 0.18 (6H, s); $^{13}C\{^1H\}$ NMR (~101 MHz, $CDCl_3$): δ_C 171.9, 163.9, 154.7, 149.3, 148.3, 137.2, 130.3, 128.7, 126.3, 122.2, 120.2, 53.5, 52.3, 37.5, 25.7, 18.2, -4.4; HRMS (ESI): *m/z* $[M+H]^+$ calcd for $C_{22}H_{31}N_2O_4Si$: 415.2053; found: 415.2074. $[\alpha]^{25}_D$ = 44.9 (c = 0.02 g/mL, $CHCl_3$). The enantiomeric ratio (er 98:2) of compound **4a**-(L) was determined by using the Daicel Chiralpak IC column, hexane/*i*-PrOH 95:05, flow rate 1.0 mL/min, UV detection at 254 nm, t_D = 47.99 min, t_L = 49.86 min.

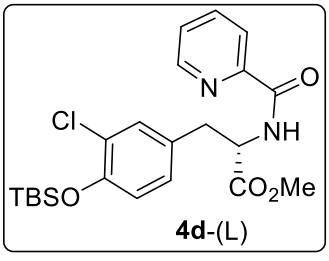
Methyl 3-(3-((tert-butyldimethylsilyl)oxy)phenyl)-2-(picolinamido)propanoate propanoate (4b-(DL)): The compound **4b**-(DL) was obtained from procedure A, B and C after purification by column chromatography on silica gel (EtOAc:hexanes = 30:70) as a colourless semi solid (654 mg, 79%, 2 mmol scale); R_f (EtOAc/hexanes = 30:70) 0.5; IR (DCM): 3385, 2953, 1745, 1486 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ_H 8.55-8.54 (2H, m,), 8.18 (1H, d, J = 7.6 Hz), 7.85 (1H, t, J = 7.2 Hz), 7.44 (1H, t, J = 5.2 Hz), 7.15 (1H, t, J = 7.8 Hz), 6.78 (1H, d, J = 7.5 Hz), 6.73-6.68 (2H, m), 5.08-5.03 (1H, m), 3.74 (3H, s), 3.26-3.16 (2H, m), 0.95 (9H, s), 0.13 (6H, s); $^{13}C\{^1H\}$ NMR (~101 MHz, $CDCl_3$): δ_C 171.7, 163.8, 155.7, 149.1, 148.1, 137.5, 129.5, 126.4, 122.4, 122.3, 121.1, 118.8, 53.4, 52.3, 38.0, 25.6, 18.1, -4.5; HRMS (ESI): *m/z* $[M+Na]^+$ calcd for $C_{22}H_{30}N_2NaO_4Si$: 437.1873; found: 437.1881.



Ethyl (*S*)-3-(4-acetoxy-3-nitrophenyl)-2-(picolinamido)propanoate (4c-(L)): The compound **4c**-(L) was obtained from procedure H after purification by column chromatography on silica gel (EtOAc:hexanes = 30:70) as a yellow coloured solid (164 mg, 85%, 0.48 mmol scale); R_f (EtOAc/hexanes = 30:70) 0.3; mp: 100-102 ^oC; IR (DCM): 3377, 2983, 1736, 1513 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ_H 8.59-8.55 (2H, m), 8.15 (1H, d, J = 7.8 Hz), 7.94 (1H, s), 7.85 (1H, t, J = 4.8 Hz), 7.51 (1H, dd, J_1 = 8.3 Hz, J_2 = 1.5 Hz), 7.46-7.43 (1H, m), 7.15 (1H, d, J = 8.3 Hz), 5.09-5.05 (1H, m), 4.23 (2H, q, J = 7.1 Hz), 3.39-3.27 (2H, m), 2.35 (3H, s), 1.26 (3H, t, J = 7.1 Hz); $^{13}C\{^1H\}$ NMR (~101 MHz, $CDCl_3$): δ_C 170.6, 168.6, 164.1, 149.0, 148.4, 143.0, 141.3, 137.4, 135.7, 126.6, 126.6, 125.3, 122.2, 62.0, 53.1, 37.4, 20.8, 14.1; HRMS (ESI): *m/z* $[M+H]^+$ calcd for $C_{19}H_{20}N_3O_7$: 402.1301; found: 402.1298. $[\alpha]^{25}_D$ = 44.2 (c = 0.03 g/mL, $CHCl_3$). The HPLC of compound **4c**-(L) was determined by using the Daicel Chiralpak IC column, hexane/*i*-PrOH 50:50, flow rate 1.0 mL/min, UV detection at 254 nm, t_D = -, t_L = 19.07 min.

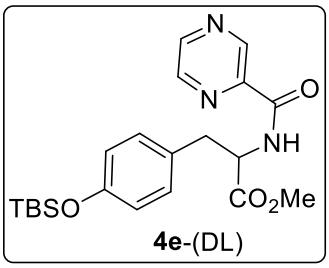


Methyl (*S*)-3-(4-((tert-butyldimethylsilyl)oxy)-3-chlorophenyl)-2-(picolinamido)propanoate (4d-(L)): The compound **4d**-(L) was obtained from procedure A, B and C after purification by column chromatography on silica gel (EtOAc:hexanes = 30:70) as a colourless semi solid (180 mg, 43%, 1 mmol scale); R_f (EtOAc/hexanes = 30:70) 0.4; IR (DCM): 3375, 2953, 1743, 1497



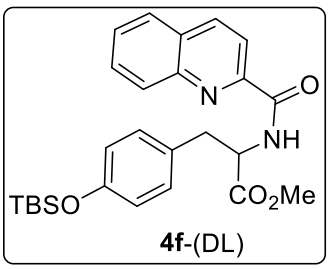
cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 8.57 (1H, d, J = 4.6 Hz), 8.49 (1H, d, J = 8.3 Hz), 8.17 (1H, d, J = 7.8 Hz), 7.85 (1H, td, J_1 = 7.6 Hz, J_2 = 1.2 Hz), 7.46-7.43 (1H, m), 7.18 (1H, d, J = 1.9 Hz), 6.95 (1H, dd, J_1 = 8.2 Hz, J_2 = 1.9 Hz), 6.80 (1H, d, J = 8.3 Hz), 5.05-5.00 (1H, m), 3.74 (3H, s), 3.17-3.15 (2H, m), 1.02 (9H, s), 0.21 (6H, s);
$^{13}C\{^{1}H\}$ NMR (~101 MHz, $CDCl_3$): δ_C 171.6, 164.0, 150.6, 149.2, 148.3, 137.3, 131.0, 129.9, 128.3, 126.4, 125.5, 122.2, 120.7, 53.4, 52.4, 37.3, 25.6, 18.3, -4.4; HRMS (ESI): *m/z* $[M+H]^+$ calcd for $C_{22}H_{30}ClN_2O_4Si$: 449.1663; found: 449.1663. $[\alpha]^{25}_D$ = 35.9 (c = 0.04 g/mL, $CHCl_3$).
The HPLC of compound **4d**-(L) was determined by using the Daicel Chiralpak IC column, hexane/*i*-PrOH 50:50, flow rate 1.0 mL/min, UV detection at 254 nm, t_D = -, t_L = 7.72 min.

Methyl 3-(4-((tert-butyldimethylsilyl)oxy)phenyl)-2-(pyrazine-2-carboxamido)propanoate (4e-(DL)): The compound **4e**-(DL) was obtained from procedure A, B and C after purification by column chromatography on silica gel (EtOAc:hexanes = 30:70) as a colourless solid (169 mg, 81%, 0.5 mmol scale); R_f (EtOAc/hexanes = 30:70) 0.3; mp: 76-78 ^{o}C; IR (DCM): 3387, 2955, 1746, 1512 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 9.38 (1H, s), 8.76 (1H, d, J = 2.4 Hz), 8.55-8.54 (1H, m), 8.20 (1H, d, J = 8.1 Hz), 7.03 (2H, d, J = 8.4 Hz), 6.77 (2H, d, J = 8.4 Hz), 5.07-5.02 (1H, m), 3.75 (3H, s), 3.24-3.15 (2H, m), 0.98 (9H, s), 0.18 (6H, s); $^{13}C\{^{1}H\}$ NMR (~101 MHz, $CDCl_3$): δ_C 171.6, 162.6, 154.8, 147.5, 144.4, 144.0, 142.7, 130.2, 128.3, 120.3, 53.4, 52.4, 37.4, 25.6, 18.2, -4.4; HRMS (ESI): *m/z* $[M+H]^+$ calcd for $C_{21}H_{30}N_3O_4Si$: 416.2006; found: 416.2014.



4e-(DL)

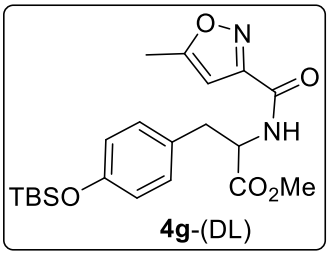
Methyl 3-(4-((tert-butyldimethylsilyl)oxy)phenyl)-2-(isoquinoline-1-carboxamido)propanoate (4f-(DL)): The compound **4f**-(DL) was obtained from procedure A, B and C after purification by column chromatography on silica gel (EtOAc:hexanes = 30:70) as a colourless solid (174 mg, 75%, 0.5 mmol scale); R_f (EtOAc/hexanes = 30:70) 0.3; mp: 118-120 ^{o}C; IR (DCM): 3387, 2953, 1744, 1502 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 8.72 (1H, d, J = 8.4 Hz), 8.28 (2H, s), 8.10 (1H, d, J = 8.5 Hz), 7.85 (1H, d, J = 8.2 Hz), 7.75 (1H, t, J = 7.2 Hz), 7.60 (1H, t, J = 7.2 Hz), 7.12 (2H, d, J = 8.4 Hz), 6.80 (2H, d, J = 8.3 Hz), 5.13-5.08 (1H, m), 3.75 (3H, s), 3.25 (2H, d, J = 7.2 Hz), 0.98 (9H, s), 0.19 (6H, s); $^{13}C\{^{1}H\}$ NMR (~101 MHz, $CDCl_3$): δ_C 171.9, 164.0, 154.7, 149.0, 146.4, 137.3, 130.3, 129.9, 129.9, 129.3, 128.6,



4f-(DL)

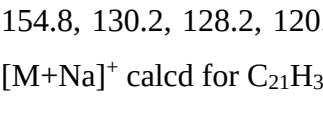
127.9, 127.6, 120.1, 118.6, 53.5, 52.2, 37.5, 26.0, 18.1, -4.5; HRMS (ESI): *m/z* $[M+H]^+$ calcd for $C_{26}H_{33}N_2O_4Si$: 465.2210; found: 465.2201.

Methyl 3-(4-((tert-butyldimethylsilyl)oxy)phenyl)-2-(5-methylisoxazole-3-carboxamido)propanoate (4g-(DL)): The compound **4g**-(DL) was obtained from procedure A, B and C after purification by column chromatography on silica gel (EtOAc:hexanes = 20:80) as a colourless semi solid (100 mg, 48%, 0.5 mmol scale); R_f (EtOAc/hexanes = 20:80) 0.5; IR (DCM): 3407, 2955, 1744, 1510 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ_H 7.22 (1H, d, *J* = 8.1 Hz), 7.02 (2H, d, *J* = 8.4 Hz), 6.77 (2H, d, *J* = 8.4 Hz), 6.41 (1H, s), 5.01-4.96 (1H, m), 3.72 (3H, s), 3.19-3.09 (2H, m), 2.47 (3H, s), 0.97 (9H, s), 0.18 (6H, s); $^{13}C\{^1H\}$ NMR (~101 MHz, $CDCl_3$): δ_C 171.3, 171.2, 158.7, 158.2, 154.8, 130.2, 128.2, 120.3, 101.3, 53.3, 52.4, 37.3, 25.6, 18.2, 12.3, -4.4; HRMS (ESI): *m/z* $[M+Na]^+$ calcd for $C_{21}H_{30}N_2NaO_5Si$: 441.1822; found: 441.1815.



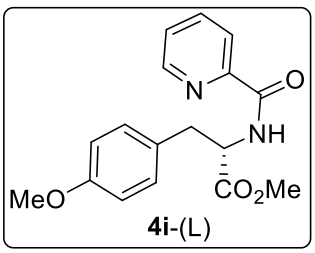
4g-(DL)

Methyl 2-benzamido-3-(4-((tert-butyldimethylsilyl)oxy)phenyl)propanoate (4h-(DL)): The compound **4h**-(DL) was obtained from procedure A, B and C after purification by column chromatography on silica gel (EtOAc:hexanes = 20:80) as a colourless semi solid (100 mg, 48%, 0.5 mmol scale); R_f (EtOAc/hexanes = 20:80) 0.5; IR (DCM): 3409, 2932, 1744, 1510 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ_H 7.74 (2H, d, *J* = 7.2 Hz), 7.51 (1H, t, *J* = 7.4 Hz), 7.43 (2H, t, *J* = 7.6 Hz), 7.01 (2H, d, *J* = 7.4 Hz), 6.79 (2H, d, *J* = 8.4 Hz), 6.67 (1H, br. s), 5.09-5.04 (1H, m), 3.76 (3H, s), 3.26-3.15 (2H, m), 0.99 (9H, s), 0.20 (6H, s); $^{13}C\{^1H\}$ NMR (~101 MHz, $CDCl_3$): δ_C 172.2, 166.9, 154.8, 133.9, 131.8, 130.3, 128.6, 128.5, 127.0, 120.3, 53.6, 52.4, 37.1, 25.7, 18.2, -4.4; HRMS (ESI): *m/z* $[M+H]^+$ calcd for $C_{23}H_{32}NO_4Si$: 414.2101; found: 414.2102.



4h-(DL)

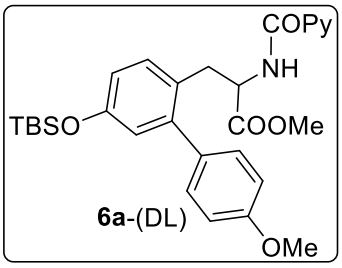
Methyl (*S*)-3-(4-methoxyphenyl)-2-(picolinamido)propanoate (4i-(L)): The compound **4i**-(L) was obtained from procedure B and C after purification by column chromatography on silica gel (EtOAc:hexanes = 30:70) as a colourless semi solid (100 mg, 32%, 1 mmol scale); R_f (EtOAc/hexanes = 30:70) 0.3; IR (DCM): 3387, 2953, 1744, 1513 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ_H 8.54 (1H, dd, J_1 = 4.7 Hz, J_2 = 0.7 Hz), 8.49 (1H, d, *J* = 8.2 Hz), 8.16 (1H, d, *J* = 7.8 Hz), 7.85-7.81 (1H, m), 7.43-7.40 (1H,



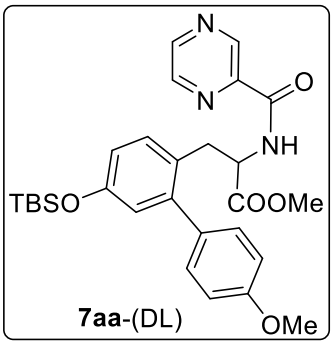
4i-(L)

m), 7.10 (2H, d, J = 8.6 Hz), 6.81 (2H, d, J = 8.6 Hz), 5.06-5.01 (1H, m), 3.76 (3H, s), 3.73 (3H, s), 3.24-3.14 (2H, m); $^{13}C\{^{1}H\}$ NMR (~101 MHz, $CDCl_3$): δ_C 171.9, 164.0, 158.6, 149.3, 148.3, 137.3, 130.3, 127.9, 126.4, 122.2, 114.0, 55.2, 53.6, 52.4, 37.4; HRMS (ESI): *m/z* $[M+H]^+$ calcd for $C_{17}H_{19}N_2O_4$: 315.1345; found: 315.1339. $[\alpha]^{25}_D$ = 53.9 (c = 0.02 g/mL, $CHCl_3$). The HPLC of compound **4i**-(L) was determined by using the Daicel Chiralpak IC column, hexane/*i*-PrOH 50:50, flow rate 1.0 mL/min, UV detection at 254 nm, t_D = -, t_L = 12.76 min.

Methyl 3-(5-((tert-butyldimethylsilyl)oxy)-4'-methoxy-[1,1'-biphenyl]-2-yl)-2-(picolinamido)propanoate (6a-(DL)): The compound **6a**-(DL) was obtained from procedure D after purification by column chromatography on silica gel (EtOAc:hexanes = 30:70) as a colourless solid (14 mg, 18%, 0.15 mmol scale); R_f (EtOAc/hexanes = 30:70) 0.35; mp: 90-92 °C; IR (DCM): 3376, 2932, 1746, 1515 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 8.57-8.55 (1H, m), 8.19 (1H, d, J = 8.3 Hz), 8.07 (1H, d, J = 7.8 Hz), 7.82 (1H, td, J_1 = 7.7 Hz, J_2 = 1.7 Hz), 7.45-7.41 (1H, m), 7.22 (2H, dt, J_1 = 8.6 Hz, J_2 = 2.8 Hz), 7.17 (1H, d, J = 8.3 Hz), 6.90 (2H, dt, J_1 = 8.6 Hz, J_2 = 2.8 Hz), 6.75 (1H, dd, J_1 = 8.3 Hz, J_2 = 2.6 Hz), 6.69 (1H, d, J = 2.6 Hz), 4.82-4.76 (1H, m), 3.85 (3H, s), 3.63 (3H, s), 3.29 (1H, dd, J_1 = 14.2 Hz, J_2 = 5.9 Hz), 3.11 (1H, dd, J_1 = 14.1 Hz, J_2 = 8.2 Hz), 0.97 (9H, s), 0.18 (6H, s); $^{13}C\{^{1}H\}$ NMR (~101 MHz, $CDCl_3$): δ_C 172.1, 163.8, 158.6, 154.2, 149.3, 148.1, 143.6, 137.1, 133.5, 130.9, 130.4, 126.6, 126.2, 122.2, 122.2, 119.0, 113.6, 55.2, 53.4, 52.2, 34.4, 25.7, 18.2, -4.4; HRMS (ESI): *m/z* $[M+H]^+$ calcd for $C_{29}H_{37}N_2O_5Si$: 521.2472; found: 521.2471.

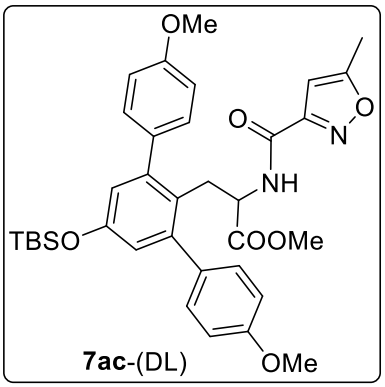


Methyl 3-(5-((tert-butyldimethylsilyl)oxy)-4'-methoxy-[1,1'-biphenyl]-2-yl)-2-(pyrazine-2-carboxamido)propanoate (7aa-(DL)): The compound **7aa**-(DL) was obtained from procedure D after purification by column chromatography on silica gel (EtOAc:hexanes = 30:70) as a colourless solid (21 mg, 27%, 0.15 mmol scale); R_f (EtOAc/hexanes = 30:70) 0.2; mp: 142-144 °C; IR (DCM): 3390, 2930, 1744, 1516 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 9.24 (1H, d, J = 0.9 Hz), 8.73 (1H, d, J = 2.4 Hz), 8.52-8.51 (1H, m), 7.89 (1H, d, J = 8.2 Hz), 7.18 (2H, d, J = 8.5 Hz), 7.11 (1H, d, J = 8.3 Hz), 6.86 (2H, d, J = 8.6 Hz), 6.72 (1H, dd, J_1 = 8.4 Hz, J_2 = 2.6 Hz), 6.67 (1H, d, J = 2.6 Hz), 4.80-4.75 (1H, m), 3.82 (3H, s), 3.63 (3H, s), 3.34 (1H, dd, J_1 = 14.2 Hz, J_2 = 5.6 Hz), 3.10 (1H, dd, J_1 = 14.2 Hz, J_2 = 8.0 Hz), 0.95 (9H, s), 0.16 (6H, s);

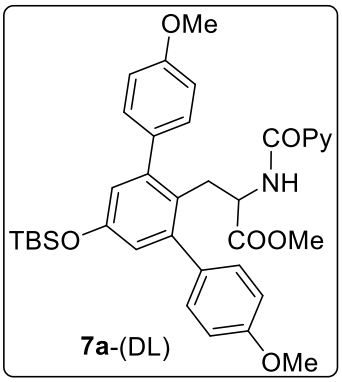


HRMS (ESI): *m/z* $[M+H]^+$ calcd for $C_{28}H_{36}N_3O_5Si$: 522.2424; found: 522.2431. $^{13}C\{^1H\}$ NMR (~101 MHz, $CDCl_3$): δ_C 171.8, 162.4, 158.7, 154.3, 147.3, 144.4, 144.0, 143.6, 142.5, 133.4, 131.0, 130.3, 126.3, 122.3, 119.0, 113.6, 55.2, 53.3, 52.3, 34.3, 25.6, 18.2, -4.4;

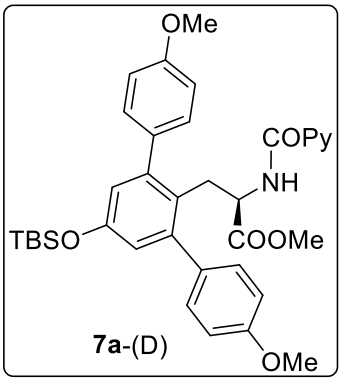
Methyl 3-(5'-((tert-butyldimethylsilyl)oxy)-4,4''-dimethoxy-[1,1':3',1''-terphenyl]-2'-yl)-2-(5-methylisoxazole-3-carboxamido)propanoate (7ac-(DL)): The compound **7ac**-(DL) was obtained from procedure D after purification by column chromatography on silica gel (EtOAc:hexanes = 20:80) as a colourless solid (51 mg, 80%, 0.1 mmol scale); R_f (EtOAc/hexanes = 20:80) 0.4; mp: 126-128 °C; IR (DCM): 3406, 2954, 1745, 1511 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ_H 7.32 (4H, d, *J* = 8.5 Hz), 7.00 (4H, d, *J* = 8.6 Hz), 6.68 (2H, s), 6.47 (1H, d, *J* = 8.6 Hz), 6.30 (1H, s), 4.36-4.30 (1H, m), 3.89 (6H, s), 3.48 (3H, s), 3.36 (1H, dd, J_1 = 14.3 Hz, J_2 = 4.6 Hz), 3.04 (1H, dd, J_1 = 14.2 Hz, J_2 = 11.0 Hz), 2.47 (3H, s), 0.97 (9H, s), 0.18 (6H, s); $^{13}C\{^1H\}$ NMR (~101 MHz, $CDCl_3$): δ_C 171.5, 170.8, 158.8, 158.6, 158.0, 153.5, 144.5, 133.9, 130.5, 124.5, 121.4, 113.9, 101.3, 55.3, 52.1, 51.9, 31.0, 25.7, 18.2, 12.3, -4.4; HRMS (ESI): *m/z* $[M+H]^+$ calcd for $C_{35}H_{43}N_2O_7Si$: 631.2840; found: 631.2854.



Methyl 3-(5'-((tert-butyldimethylsilyl)oxy)-4,4''-dimethoxy-[1,1':3',1''-terphenyl]-2'-yl)-2-(picolinamido)propanoate (7a-(DL)): The compound **7a**-(DL) was obtained from procedure D after purification by column chromatography on silica gel (EtOAc:hexanes = 30:70) as a colourless solid (73 mg, 78%, 0.15 mmol scale); R_f (EtOAc/hexanes = 30:70) 0.4; mp: 126-128 °C; IR (DCM): 3388, 2954, 1744, 1512 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ_H 8.58 (1H, d, *J* = 4.7 Hz), 8.03 (1H, d, *J* = 7.8 Hz), 7.82-7.74 (2H, m), 7.44-7.41 (1H, m), 7.33 (4H, d, *J* = 8.7 Hz), 7.00 (4H, d, *J* = 8.6 Hz), 6.67 (2H, s), 4.43-4.37 (1H, m), 3.89 (6H, s), 3.49 (3H, s), 3.42 (1H, dd, J_1 = 14.2 Hz, J_2 = 4.5 Hz), 3.13 (1H, dd, J_1 = 14.2 Hz, J_2 = 11.0 Hz), 0.95 (9H, s), 0.16 (3H, s), 0.16 (3H, s); $^{13}C\{^1H\}$ NMR (~101 MHz, $CDCl_3$): δ_C 172.0, 163.7, 158.6, 153.3, 149.2, 147.7, 144.4, 137.0, 134.0, 130.5, 126.1, 124.9, 122.1, 121.3, 113.7, 55.2, 52.1, 51.9, 31.1, 25.6, 18.1, -4.5; HRMS (ESI): *m/z* $[M+H]^+$ calcd for $C_{36}H_{43}N_2O_6Si$: 627.2890; found: 627.2890. The HPLC of compound **7a**-(DL) was determined

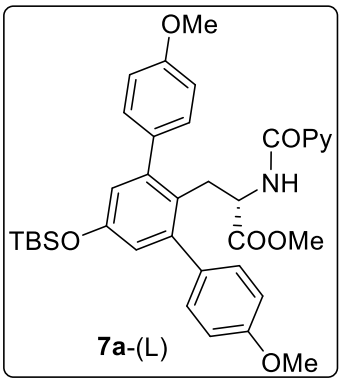


by using the Daicel Chiralpak IA column, hexane/*i*-PrOH 90:10, flow rate 1.0 mL/min, UV detection at 254 nm, t_D = 8.66 min, t_L = 9.85 min.

Methyl (*R*)-3-(5'-((tert-butyldimethylsilyl)oxy)-4,4''-dimethoxy-[1,1':3',1''-terphenyl]-2'-yl)-2-(picolinamido)propanoate (7a-(D)): 

7a-(D)

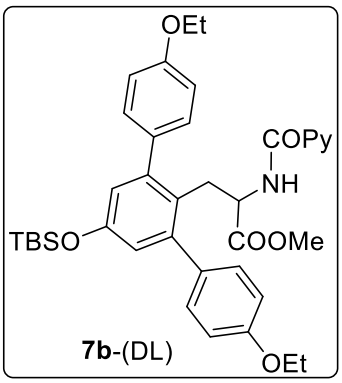
The compound **7a**-(D) was obtained from procedure D after purification by column chromatography on silica gel (EtOAc:hexanes = 30:70) as a colourless solid (71 mg, 76%, 0.15 mmol scale); R_f (EtOAc/hexanes = 30:70) 0.4; mp: 124-126 °C; IR (DCM): 3386, 2954, 1744, 1512 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ_H 8.56-8.55 (1H, m), 8.00 (1H, d, J = 7.8 Hz), 7.77 (1H, td, J_1 = 7.7 Hz, J_2 = 1.7 Hz), 7.72 (1H, d, J = 8.8 Hz), 7.42-7.38 (1H, m), 7.30 (4H, d, J = 8.6 Hz), 6.97 (4H, d, J = 8.7 Hz), 6.63 (2H, s), 4.40-4.34 (1H, m), 3.87 (6H, s), 3.46 (3H, s), 3.39 (1H, dd, J_1 = 14.2 Hz, J_2 = 4.4 Hz), 3.10 (1H, dd, J_1 = 14.2 Hz, J_2 = 11.0 Hz), 0.92 (9H, s), 0.13 (3H, s), 0.13 (3H, s); $^{13}C\{^1H\}$ NMR (~101 MHz, $CDCl_3$): δ_C 172.1, 163.8, 158.7, 153.4, 149.3, 147.8, 144.5, 137.1, 134.1, 130.6, 126.2, 125.0, 122.2, 121.4, 113.8, 55.3, 52.2, 52.0, 31.2, 25.7, 18.2, -4.4; HRMS (ESI): *m/z* $[M+H]^+$ calcd for $C_{36}H_{43}N_2O_6Si$: 627.2890; found: 627.2902. $[\alpha]^{25}_D$ = 24.9 (c = 0.02 g/mL, $CHCl_3$). The enantiomeric ratio (er 98:2) compound **7a**-(D) was determined by using the Daicel Chiralpak IA column, hexane/*i*-PrOH 90:10, flow rate 1.0 mL/min, UV detection at 254 nm, t_D = 8.99 min, t_L = 10.38 min.

Methyl (*S*)-3-(5'-((tert-butyldimethylsilyl)oxy)-4,4''-dimethoxy-[1,1':3',1''-terphenyl]-2'-yl)-2-(picolinamido)propanoate (7a-(L)): 

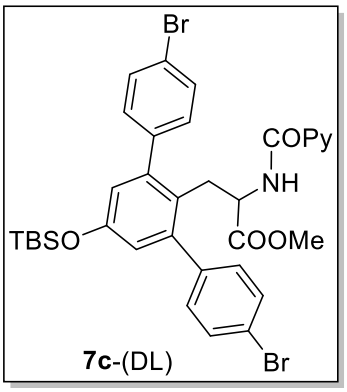
7a-(L)

The compound **7a**-(L) was obtained from procedure D after purification by column chromatography on silica gel (EtOAc:hexanes = 30:70) as a colourless solid (70 mg, 75%, 0.15 mmol scale); R_f (EtOAc/hexanes = 30:70) 0.4; mp: 124-126 °C; IR (DCM): 3378, 2954, 1744, 1511 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ_H 8.56-8.55 (1H, m), 8.00 (1H, d, J = 7.8 Hz), 7.78 (1H, td, J_1 = 7.7 Hz, J_2 = 1.7 Hz), 7.72 (1H, d, J = 8.8 Hz), 7.42-7.39 (1H, m), 7.29 (4H, d, J = 8.6 Hz), 6.97 (4H, d, J = 8.7 Hz), 6.63 (2H, s), 4.39-4.33 (1H, m), 3.87 (6H, s), 3.46 (3H, s), 3.38 (1H, dd, J_1 = 14.2 Hz, J_2 = 4.4 Hz), 3.09 (1H, dd, J_1 = 14.2 Hz, J_2 = 11.0 Hz), 0.92 (9H, s), 0.13 (3H, s), 0.12 (3H, s); $^{13}C\{^1H\}$ NMR (~101 MHz, $CDCl_3$): δ_C 172.0, 163.8, 158.7, 153.4, 149.3, 147.8, 144.5, 137.1, 134.0, 130.6, 126.1, 124.9, 122.2, 121.3, 113.7, 55.3, 52.1, 52.0, 31.1, 25.6, 18.1, -4.4; HRMS (ESI): *m/z* $[M+H]^+$ calcd for $C_{36}H_{43}N_2O_6Si$: 627.2890; found: 627.2908. $[\alpha]^{25}_D$ = -19.9 (c =

0.02 g/mL, $CHCl_3$). The enantiomeric ratio (er 97:3) compound **7a**-(L) was determined by using the Daicel Chiralpak IA column, hexane/*i*-PrOH 90:10, flow rate 1.0 mL/min, UV detection at 254 nm, t_D = 9.32 min, t_L = 10.58 min.

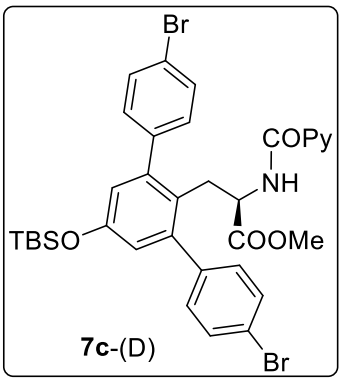
Methyl 3-(5'-((tert-butyldimethylsilyl)oxy)-4,4''-diethoxy-[1,1':3',1''-terphenyl]-2'-yl)-2-(picolinamido)propanoate (7b-(DL)): 

The compound **7b**-(DL) was obtained from procedure D after purification by column chromatography on silica gel (EtOAc:hexanes = 30:70) as a colourless solid (44 mg, 68%, 0.1 mmol scale); R_f (EtOAc/hexanes = 30:70) 0.4; mp: 138-140 ^oC; IR (DCM): 3379, 2953, 1743, 1510 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ_H 8.58 (1H, d, J = 4.3 Hz), 8.03 (1H, d, J = 7.8 Hz), 7.80 (1H, td, J_1 = 7.7 Hz, J_2 = 1.7 Hz), 7.75 (1H, d, J = 8.8 Hz), 7.44-7.41 (1H, m), 7.31 (4H, d, J = 8.6 Hz), 6.98 (4H, d, J = 8.6 Hz), 6.66 (2H, s), 4.43-4.37 (1H, m), 4.12 (4H, q, J = 7.0 Hz), 3.48 (3H, s), 3.42 (1H, dd, J_1 = 14.2 Hz, J_2 = 4.4 Hz), 3.12 (1H, dd, J_1 = 14.2 Hz, J_2 = 11.0 Hz), 1.48 (6H, t, J = 7.0 Hz), 0.94 (9H, s), 0.15 (3H, s), 0.15 (3H, s); $^{13}C\{^1H\}$ NMR (~101 MHz, $CDCl_3$): δ_C 172.1, 163.8, 158.1, 153.4, 149.3, 147.8, 144.5, 137.1, 133.9, 130.6, 126.1, 125.0, 122.2, 121.3, 114.3, 63.4, 52.2, 52.0, 31.2, 25.7, 18.2, 14.9, -4.4; HRMS (ESI): *m/z* $[M+H]^+$ calcd for $C_{38}H_{47}N_2O_6Si$: 655.3203; found: 655.3202.

Methyl 3-(4,4''-dibromo-5'-((tert-butyldimethylsilyl)oxy)-[1,1':3',1''-terphenyl]-2'-yl)-2-(picolinamido)propanoate (7c-(DL)): 

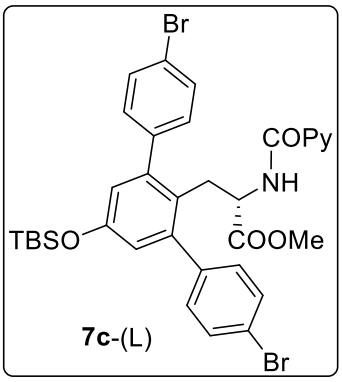
The compound **7c**-(DL) was obtained from procedure D after purification by column chromatography on silica gel (EtOAc:hexanes = 30:70) as a colourless solid (50 mg, 50%, 0.15 mmol scale); R_f (EtOAc/hexanes = 30:70) 0.6; mp: 147-149 ^oC; IR (DCM): 3379, 2930, 1744, 1513 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ_H 8.59 (1H, d, J = 4.4 Hz), 8.02 (1H, d, J = 7.8 Hz), 7.82 (1H, td, J_1 = 7.7 Hz, J_2 = 1.2 Hz), 7.74 (1H, d, J = 9.2 Hz), 7.57 (4H, d, J = 8.2 Hz), 7.47-7.44 (1H, m), 7.25 (4H, d, J = 8.2 Hz), 6.64 (2H, s), 4.44-4.38 (1H, m), 3.50 (3H, s), 3.33 (1H, dd, J_1 = 14.2 Hz, J_2 = 4.0 Hz), 3.01 (1H, dd, J_1 = 14.3 Hz, J_2 = 11.0 Hz), 0.94 (9H, s), 0.15 (3H, s), 0.15 (3H, s); $^{13}C\{^1H\}$ NMR (~101 MHz, $CDCl_3$): δ_C 171.7, 163.7, 153.7, 149.1, 147.9, 143.8, 140.3, 137.2, 131.5, 131.2, 126.3, 124.4, 122.3, 121.5, 121.5, 52.2, 31.3, 25.6, 18.2, -4.4; HRMS (ESI): *m/z* $[M+H]^+$ calcd for $C_{34}H_{37}Br_2N_2O_4Si$: 723.0889; found: 723.0875. The HPLC of compound **7c**-

(DL) was determined by using the Daicel Chiralpak IC column, hexane/*i*-PrOH 95:05, flow rate 1.0 mL/min, UV detection at 254 nm, t_D = 18.78 min, t_L = 22.74 min.



7c-(D)

Methyl (*R*)-3-(4,4''-dibromo-5'-((tert-butyldimethylsilyl)oxy)-[1,1':3',1''-terphenyl]-2'- yl)-2-(picolinamido)propanoate (7c-(D)): The compound **7c**-(D) was obtained from procedure D after purification by column chromatography on silica gel (EtOAc:hexanes = 30:70) as a colourless solid (36 mg, 50%, 0.10 mmol scale); R_f (EtOAc/hexanes = 30:70) 0.6; mp: 146-148 ^oC; IR (DCM): 3387, 2952, 1744, 1514 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ_H 8.59 (1H, d, J = 4.6 Hz), 8.02 (1H, d, J = 7.8 Hz), 7.82 (1H, td, J_1 = 7.7 Hz, J_2 = 1.6 Hz), 7.74 (1H, d, J = 9.3 Hz), 7.57 (4H, d, J = 8.4 Hz), 7.47-7.44 (1H, m), 7.25 (4H, d, J = 8.3 Hz), 6.64 (2H, s), 4.45-4.38 (1H, m), 3.50 (3H, s), 3.34 (1H, dd, J_1 = 14.4 Hz, J_2 = 4.0 Hz), 3.01 (1H, dd, J_1 = 14.4 Hz, J_2 = 11.0 Hz), 0.94 (9H, s), 0.16 (3H, s), 0.15 (3H, s); $^{13}C\{^1H\}$ NMR (~101 MHz, $CDCl_3$): δ_C 171.7, 163.7, 153.6, 149.1, 147.9, 143.8, 140.3, 137.2, 131.5, 131.2, 126.3, 124.4, 122.3, 121.5, 121.5, 52.2, 31.3, 25.6, 18.2, -4.4; HRMS (ESI): *m/z* $[M+H]^+$ calcd for $C_{34}H_{37}Br_2N_2O_4Si$: 723.0889; found: 723.0887. $[\alpha]^{25}_D$ = 18.9 (c = 0.02 g/mL, $CHCl_3$). The enantiomeric ratio (er 98:2) compound **7c**-(D) was determined by using the Daicel Chiralpak IC column, hexane/*i*-PrOH 95:05, flow rate 1.0 mL/min, UV detection at 254 nm, t_D = 17.54 min, t_L = 21.51 min.

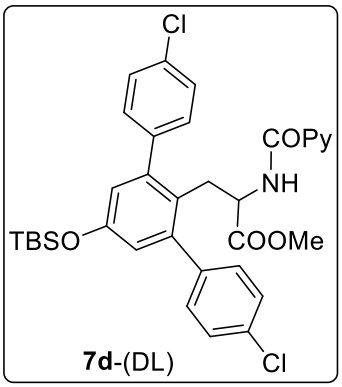


7c-(L)

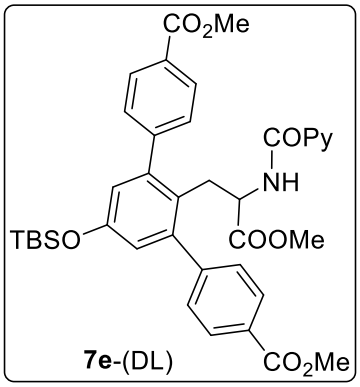
Methyl (*S*)-3-(4,4''-dibromo-5'-((tert-butyldimethylsilyl)oxy)-[1,1':3',1''-terphenyl]-2'-yl)-2-(picolinamido)propanoate (7c-(L)): The compound **7c**-(L) was obtained from procedure D after purification by column chromatography on silica gel (EtOAc:hexanes = 30:70) as a colourless solid (62 mg, 57%, 0.15 mmol scale); R_f (EtOAc/hexanes = 30:70) 0.6; mp: 147-149 ^oC; IR (DCM): 3376, 2931, 1742, 1515 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ_H 8.59 (1H, d, J = 4.6 Hz), 8.02 (1H, d, J = 7.8 Hz), 7.84-7.80 (1H, m), 7.74 (1H, d, J = 9.2 Hz), 7.57 (4H, d, J = 8.2 Hz), 7.47-7.44 (1H, m), 7.25 (4H, d, J = 8.2 Hz), 6.64 (2H, s), 4.45-4.39 (1H, m), 3.50 (3H, s), 3.34 (1H, dd, J_1 = 14.4 Hz, J_2 = 3.9 Hz), 3.02 (1H, dd, J_1 = 14.3 Hz, J_2 = 11.0 Hz), 0.94 (9H, s), 0.16 (3H, s), 0.15 (3H, s); $^{13}C\{^1H\}$ NMR (~101 MHz, $CDCl_3$): δ_C 171.7, 163.7, 153.7, 149.1, 147.9, 143.8, 140.3, 137.2, 131.5, 131.2, 126.3, 124.4, 122.3, 121.5, 121.5, 52.2, 31.3, 25.6, 18.2, -4.4; HRMS (ESI): *m/z* $[M+H]^+$ calcd for

$C_{34}H_{37}Br_2N_2O_4Si$: 723.0889; found: 723.0888. $[\alpha]^{25}_D$ = -19.9 (c = 0.02 g/mL, $CHCl_3$). The enantiomeric ratio (er 98:2) compound **7c**-(L) was determined by using the Daicel Chiralpak IC column, hexane/*i*-PrOH 95:05, flow rate 1.0 mL/min, UV detection at 254 nm, t_D = 17.34 min, t_L = 22.03 min.

Methyl 3-(5'-((tert-butyldimethylsilyl)oxy)-4,4''-dichloro-[1,1':3',1''-terphenyl]-2'-yl)-2-(picolinamido)propanoate (7d-(DL)): The compound **7d**-(DL) was obtained from procedure D after purification by column chromatography on silica gel (EtOAc:hexanes = 30:70) as a colourless solid (50 mg, 53%, 0.15 mmol scale); R_f (EtOAc/hexanes = 30:70) 0.7; mp: 180-182 ^oC; IR (DCM): 3375, 2953, 1746, 1514 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ_H 8.56 (1H, d, J = 4.6 Hz), 8.00 (1H, d, J = 7.8 Hz), 7.80 (1H, td, J_1 = 7.7 Hz, J_2 = 1.5 Hz), 7.71 (1H, d, J = 9.2 Hz), 7.45-7.38 (1H, m), 7.39 (4H, d, J = 8.3 Hz), 7.28 (4H, d, J = 8.3 Hz), 6.62 (2H, s), 4.42-4.36 (1H, m), 3.48 (3H, s), 3.31 (1H, dd, J_1 = 14.4 Hz, J_2 = 4.1 Hz), 2.99 (1H, dd, J_1 = 14.3 Hz, J_2 = 10.9 Hz), 0.92 (9H, s), 0.13 (3H, s), 0.13 (3H, s); $^{13}C\{^1H\}$ NMR (~101 MHz, $CDCl_3$): δ_C 171.7, 163.7, 153.6, 149.1, 147.9, 143.8, 139.9, 137.2, 133.3, 130.9, 128.6, 126.3, 124.5, 122.3, 121.5, 52.2, 31.3, 25.6, 18.2, -4.4; HRMS (ESI): *m/z* $[M+H]^+$ calcd for $C_{34}H_{37}Cl_2N_2O_4Si$: 635.1900; found: 635.1901.

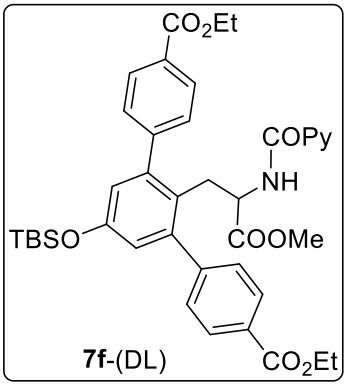


Dimethyl 5'-((tert-butyldimethylsilyl)oxy)-2'-(3-methoxy-3-oxo-2-(picolinamido)propyl)-[1,1':3',1''-terphenyl]-4,4''-dicarboxylate (7e-(DL)): The compound **7e**-(DL) was obtained from procedure D after purification by column chromatography on silica gel (EtOAc:hexanes = 30:70) as a colourless solid (60 mg, 53%, 0.15 mmol scale); R_f (EtOAc/hexanes = 30:70) 0.3; mp: 150-152 ^oC; IR (DCM): 3374, 2953, 1722, 1275 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ_H 8.59 (1H, d, J = 4.6 Hz), 8.12 (4H, d, J = 8.3 Hz), 8.01 (1H, d, J = 7.8 Hz), 7.82 (1H, td, J_1 = 7.7 Hz, J_2 = 1.7 Hz), 7.70 (1H, d, J = 8.3 Hz), 7.46 (4H, d, J = 8.1 Hz), 7.47-7.45 (1H, m), 6.67 (2H, s), 4.41-4.34 (1H, m), 3.99 (6H, s), 3.44 (3H, s), 3.37 (1H, dd, J_1 = 14.4 Hz, J_2 = 4.2 Hz), 3.01 (1H, dd, J_1 = 14.4 Hz, J_2 = 11.1 Hz), 0.95 (9H, s), 0.16 (3H, s), 0.16 (3H, s); $^{13}C\{^1H\}$ NMR (~101 MHz, $CDCl_3$): δ_C 171.5, 167.0, 163.7, 153.7, 149.1, 148.0, 146.2, 144.1, 137.2, 129.7, 129.7, 129.0,

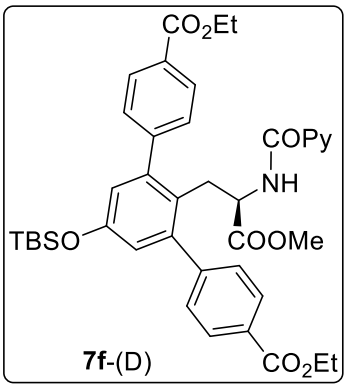


126.3, 124.1, 122.2, 121.4, 52.2, 52.2, 31.4, 25.6, 18.2, -4.4; HRMS (ESI): *m/z* $[M+Na]^+$ calcd for $C_{38}H_{42}N_2NaO_8Si$: 705.2608; found: 705.2603.

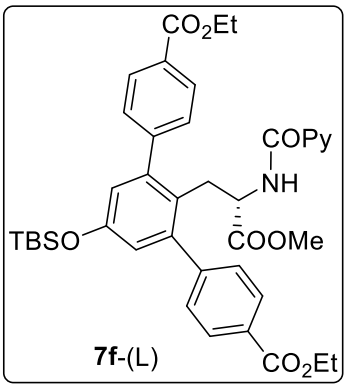
Diethyl 5'-((tert-butyldimethylsilyl)oxy)-2'-(3-methoxy-3-oxo-2-(picolinamido)propyl)-[1,1':3',1''-terphenyl]-4,4''-dicarboxylate (7f-(DL)): The compound **7f**-(DL) was obtained from procedure D after purification by column chromatography on silica gel (EtOAc:hexanes = 30:70) as a colourless solid (42 mg, 59%, 0.1 mmol scale); R_f (EtOAc/hexanes = 30:70) 0.3; mp: 112-114ºC; IR (DCM): 3382, 2930, 1718, 1273 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ_H 8.58 (1H, d, J = 4.5 Hz), 8.13 (4H, d, J = 7.9 Hz), 8.01 (1H, d, J = 7.8 Hz), 7.81 (1H, t, J = 7.6 Hz), 7.71 (1H, d, J = 9.2 Hz), 7.46 (4H, d, J = 7.8 Hz), 7.47-7.45 (1H, m), 6.67 (2H, s), 4.44 (4H, q, J = 7.1 Hz), 4.40-4.37 (1H, m), 3.44 (3H, s), 3.37 (1H, dd, J_1 = 14.4 Hz, J_2 = 4.1 Hz), 3.02 (1H, dd, J_1 = 14.2 Hz, J_2 = 11.1 Hz), 1.45 (6H, t, J = 7.1 Hz), 0.94 (9H, s), 0.16 (3H, s), 0.15 (3H, s); $^{13}C\{^1H\}$ NMR (~101 MHz, $CDCl_3$): δ_C 171.6, 166.5, 163.7, 153.7, 149.1, 148.0, 146.0, 144.1, 137.2, 129.7, 129.6, 129.4, 126.3, 124.1, 122.2, 121.4, 61.0, 52.1, 31.4, 25.6, 18.2, 14.4, -4.4; HRMS (ESI): *m/z* $[M+Na]^+$ calcd for $C_{40}H_{46}N_2NaO_8Si$: 733.2921; found: 733.2916. The HPLC of compound **7f**-(DL) was determined by using the Daicel Chiralpak IA column, hexane/*i*-PrOH 95:05, flow rate 1.0 mL/min, UV detection at 254 nm, t_D = 29.37 min, t_L = 19.58 min.



Diethyl (*R*)-5'-((tert-butyldimethylsilyl)oxy)-2'-(3-methoxy-3-oxo-2-(picolinamido)propyl)-[1,1':3',1''-terphenyl]-4,4''-dicarboxylate (7f-(D)): The compound **7f**-(D) was obtained from procedure D after purification by column chromatography on silica gel (EtOAc:hexanes = 30:70) as a colourless solid (46 mg, 65%, 0.1 mmol scale); R_f (EtOAc/hexanes = 30:70) 0.3; mp: 112-114 ºC; IR (DCM): 3388, 2930, 1718, 1204 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ_H 8.58 (1H, d, J = 4.6 Hz), 8.13 (4H, d, J = 8.0 Hz), 8.01 (1H, d, J = 7.8 Hz), 7.82 (1H, t, J = 7.6 Hz), 7.71 (1H, d, J = 9.2 Hz), 7.46 (4H, d, J = 7.8 Hz), 7.46-7.45 (1H, m), 6.67 (2H, s), 4.44 (4H, q, J = 7.1 Hz), 4.41-4.37 (1H, m), 3.44 (3H, s), 3.37 (1H, dd, J_1 = 14.4 Hz, J_2 = 4.1 Hz), 3.02 (1H, dd, J_1 = 14.2 Hz, J_2 = 11.1 Hz), 1.45 (6H, t, J = 7.1 Hz), 0.94 (9H, s), 0.16 (3H, s), 0.15 (3H, s); $^{13}C\{^1H\}$ NMR (~101 MHz, $CDCl_3$): δ_C 171.6, 166.5, 163.7, 153.7, 149.1, 148.0, 146.0, 144.1, 137.2, 129.7, 129.6, 129.4,

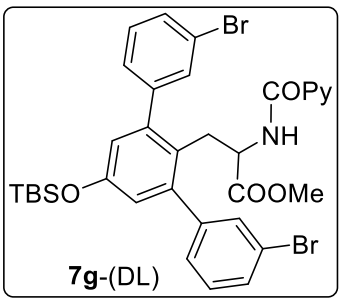


126.3, 124.1, 122.2, 121.4, 61.0, 52.1, 31.3, 25.6, 18.2, 14.4, -4.4; HRMS (ESI): *m/z* $[M+Na]^+$ calcd for $C_{40}H_{46}N_2NaO_8Si$: 733.2921; found: 733.2921. $[\alpha]^{25}_D$ = 29.9 (c = 0.02 g/mL, $CHCl_3$). The enantiomeric ratio (er 98:02) compound **7f**-(D) was determined by using the Daicel Chiralpak IA column, hexane/*i*-PrOH 95:05, flow rate 1.0 mL/min, UV detection at 254 nm, t_D = 29.39 min, t_L = 19.88 min.



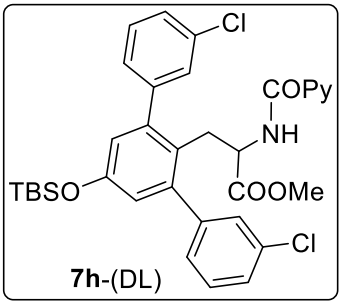
Diethyl (*S*)-5'-((tert-butyldimethylsilyl)oxy)-2'-(3-methoxy-3-oxo-2- (picolinamido)propyl)-[1,1':3',1''-terphenyl]-4,4''-dicarboxylate (7f-(L)): The compound **7f**-(L) was obtained from procedure D after purification by column chromatography on silica gel (EtOAc:hexanes = 30:70) as a colourless solid (40 mg, 56%, 0.1 mmol scale); R_f (EtOAc/hexanes = 30:70) 0.3; mp: 110-112°C; IR (DCM): 3377, 2930, 1717, 1273 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ_H 8.58 (1H, d, *J* = 4.6 Hz), 8.13 (4H, d, *J* = 8.1 Hz), 8.01 (1H, d, *J* = 7.8 Hz), 7.82 (1H, td, J_1 = 7.6 Hz, J_2 = 1.3 Hz), 7.71 (1H, d, *J* = 9.2 Hz), 7.46 (4H, d, *J* = 8.0 Hz), 7.46-7.45 (1H, m), 6.67 (2H, s), 4.44 (4H, q, *J* = 7.1 Hz), 4.41-4.35 (1H, m), 3.44 (3H, s), 3.37 (1H, dd, J_1 = 14.4 Hz, J_2 = 4.2 Hz), 3.02 (1H, dd, J_1 = 14.3 Hz, J_2 = 11.0 Hz), 1.45 (6H, t, *J* = 7.1 Hz), 0.94 (9H, s), 0.16 (3H, s), 0.15 (3H, s); $^{13}C\{^1H\}$ NMR (~101 MHz, $CDCl_3$): δ_C 171.6, 166.5, 163.7, 153.7, 149.1, 148.0, 146.0, 144.1, 137.2, 129.7, 129.6, 129.4, 126.3, 124.1, 122.2, 121.4, 61.0, 52.1, 31.4, 25.6, 18.2, 14.4, -4.4; HRMS (ESI): *m/z* $[M+Na]^+$ calcd for $C_{40}H_{46}N_2NaO_8Si$: 733.2921; found: 733.2928. $[\alpha]^{25}_D$ = -31.9 (c = 0.02 g/mL, $CHCl_3$). The enantiomeric ratio (er 98:02) compound **7f**-(L) was determined by using the Daicel Chiralpak IA column, hexane/*i*-PrOH 95:05, flow rate 1.0 mL/min, UV detection at 254 nm, t_D = 30.41 min, t_L = 19.45 min.

Methyl 3-(3,3''-dibromo-5'-((tert-butyldimethylsilyl)oxy)-[1,1':3',1''-terphenyl]-2'-yl)-2-(picolinamido)propanoate (7g-(DL)): The compound **7g**-(DL) was obtained from procedure D after purification by column chromatography on silica gel (EtOAc:hexanes = 30:70) as a colourless solid (65 mg, 60%, 0.15 mmol scale); R_f (EtOAc/hexanes = 30:70) 0.65; mp: 205-207 °C; IR (DCM): 3386, 2953, 1742, 1513 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ_H 8.64 (1H, d, *J* = 4.2 Hz), 8.00 (1H, d, *J* = 7.8 Hz), 7.80-7.76 (2H, m), 7.54-7.50 (4H, m), 7.43-7.40 (1H, m), 7.31-7.30 (4H, m), 6.64 (2H, s), 4.44-4.38 (1H, m), 3.50 (3H, s), 3.38 (1H, dd,



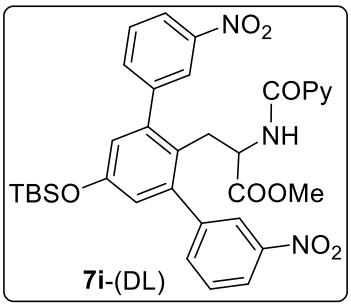
J_1 = 14.4 Hz, J_2 = 4.1 Hz), 3.00 (1H, dd, J_1 = 14.4 Hz, J_2 = 11.0 Hz), 0.93 (9H, s), 0.14 (3H, s), 0.13 (3H, s); $^{13}C\{^1H\}$ NMR (~101 MHz, $CDCl_3$): δ_C 171.7, 163.8, 153.7, 149.1, 148.3, 143.5, 143.4, 137.1, 132.3, 130.4, 130.0, 128.4, 126.2, 124.4, 122.5, 122.2, 121.6, 52.3, 52.0, 31.5, 25.6, 18.1, -4.4; HRMS (ESI): *m/z* $[M+H]^+$ calcd for $C_{34}H_{37}Br_2N_2O_4Si$: 723.0889; found: 723.0881.

Methyl 3-(5'-((tert-butyldimethylsilyl)oxy)-3,3''-dichloro-[1,1':3',1''-terphenyl]-2'-yl)-2-(picolinamido)propanoate propanoate (7h-(DL)): The compound **7h-**(DL) was obtained from procedure D after purification by column chromatography on silica gel (EtOAc:hexanes = 30:70) as a colourless solid (32 mg, 51%, 0.1 mmol scale); R_f (EtOAc/hexanes = 30:70) 0.55; mp: 202-204 ^oC; IR (DCM): 3385, 2953, 1744, 1513 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ_H 8.64 (1H, d, J = 4.5 Hz), 8.03 (1H, d, J = 7.8 Hz), 7.81-7.77 (2H, m), 7.45-7.39 (7H, m), 7.31-7.27 (2H, m), 6.66 (2H, s), 4.46-4.42 (1H, m), 3.51 (3H, s), 3.40 (1H, dd, J_1 = 14.4 Hz, J_2 = 4.1 Hz), 3.02 (1H, dd, J_1 = 14.4 Hz, J_2 = 11.0 Hz), 0.95 (9H, s), 0.16 (3H, s), 0.16 (3H, s); $^{13}C\{^1H\}$ NMR (~101 MHz, $CDCl_3$): δ_C 171.7, 163.8, 153.7, 149.1, 148.3, 143.6, 143.2, 137.1, 134.2, 129.7, 129.5, 127.9, 127.5, 126.2, 124.4, 122.2, 121.6, 52.2, 52.1, 31.5, 25.6, 18.1, -4.4; HRMS (ESI): *m/z* $[M+H]^+$ calcd for $C_{34}H_{37}Cl_2N_2O_4Si$: 635.1900; found: 635.1908.



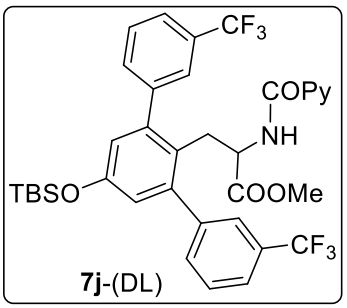
7h-(DL)

Methyl 3-(5'-((tert-butyldimethylsilyl)oxy)-3,3''-dinitro-[1,1':3',1''-terphenyl]-2'-yl)-2-(picolinamido)propanoate (7i-(DL)): The compound **7i-**(DL) was obtained from procedure D after purification by column chromatography on silica gel (EtOAc:hexanes = 30:70) as a yellow coloured solid (62 mg, 63%, 0.15 mmol scale); R_f (EtOAc/hexanes = 30:70) 0.2; mp: 217-219 ^oC; IR (DCM): 3383, 2954, 1743, 1526 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ_H 8.52 (1H, d, J = 4.5 Hz), 8.28 (2H, d, J = 9.3 Hz), 8.24 (2H, br. s), 7.98 (1H, d, J = 7.8 Hz), 7.81-7.73 (4H, m), 7.65 (2H, t, J = 7.9 Hz), 7.46-7.42 (1H, m), 6.70 (2H, s), 4.39-4.33 (1H, m), 3.44 (3H, s), 3.34 (1H, dd, J_1 = 14.5 Hz, J_2 = 4.3 Hz), 2.99 (1H, dd, J_1 = 14.5 Hz, J_2 = 10.9 Hz), 0.94 (9H, s), 0.16 (3H, s), 0.15 (3H, s); $^{13}C\{^1H\}$ NMR (~101 MHz, $CDCl_3$): δ_C 171.3, 163.6, 154.1, 148.7, 148.3, 148.2, 142.8, 142.8, 137.3, 135.9, 129.6, 126.5, 124.3, 124.2, 122.5, 122.2, 122.1, 52.4, 51.8, 31.8, 25.6, 18.2, -4.4; HRMS (ESI): *m/z* $[M+H]^+$ calcd for $C_{34}H_{37}N_4O_8Si$: 657.2381; found: 657.2384.

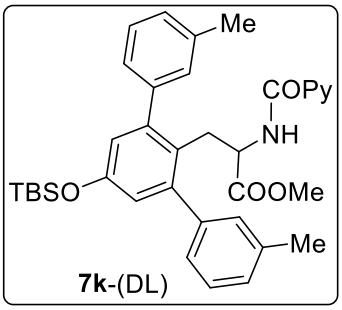


7i-(DL)

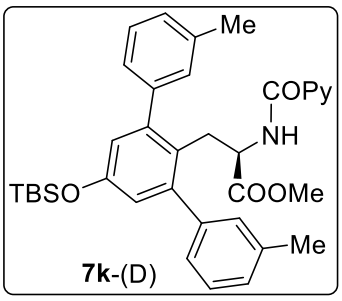
Methyl 3-(5'-((tert-butyldimethylsilyl)oxy)-3,3''-bis(trifluoromethyl)-[1,1':3',1''-terphenyl]-2'-yl)-2-(picolinamido)propanoate (7j-(DL)): The compound **7j**-(DL) was obtained from procedure D after purification by column chromatography on silica gel (EtOAc:hexanes = 30:70) as a colourless solid (57 mg, 55%, 0.15 mmol scale); R_f (EtOAc/hexanes = 30:70) 0.4; mp: 141-143 °C; IR (DCM): 3390, 2954, 1745, 1513 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ_H 8.56 (1H, d, J = 4.7 Hz), 8.02 (1H, d, J = 7.8 Hz), 7.83-7.78 (2H, m), 7.69-7.60 (8H, m), 7.46-7.42 (1H, m), 6.70 (2H, s), 4.42-4.36 (1H, m), 3.47 (3H, s), 3.40 (1H, dd, J_1 = 14.4 Hz, J_2 = 3.9 Hz), 2.96 (1H, dd, J_1 = 14.4 Hz, J_2 = 11.1 Hz), 0.96 (9H, s), 0.18 (3H, s), 0.17 (3H, s); $^{13}C\{^1H\}$ NMR (~101 MHz, $CDCl_3$): δ_C 171.6, 163.7, 153.8, 149.0, 148.1, 143.6, 142.1, 137.1, 133.3, 130.7 (q, J_{C-F} = 32.1 Hz), 129.1, 126.3, 126.0 (q, J_{C-F} = 3.6 Hz), 124.4, 124.2 (q, J_{C-F} = 3.3 Hz), 124.1 (q, J_{C-F} = 270.6 Hz), 122.2, 121.8, 52.1, 51.8, 31.8, 25.6, 18.1, -4.4; $^{19}F\{^1H\}$ NMR (~376 MHz, $CDCl_3$): δ_F = -62.4; HRMS (ESI): *m/z* $[M+H]^+$ calcd for $C_{36}H_{37}F_6N_2O_4Si$: 703.2427; found: 703.2431.



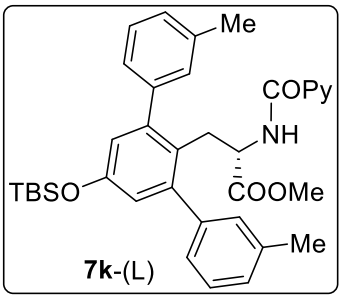
Methyl 3-(5'-((tert-butyldimethylsilyl)oxy)-3,3''-dimethyl-[1,1':3',1''-terphenyl]-2'-yl)-2-(picolinamido)propanoate propanoate (7k-(DL)): The compound **7k**-(DL) was obtained from procedure D after purification by column chromatography on silica gel (EtOAc:hexanes = 30:70) as a colourless solid (65 mg, 73%, 0.15 mmol scale); R_f (EtOAc/hexanes = 30:70) 0.6; mp: 172-174 °C; IR (DCM): 3380, 2953, 1743, 1513 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ_H 8.58 (1H, d, J = 4.4 Hz), 8.06 (1H, d, J = 7.8 Hz), 7.82-7.76 (2H, m), 7.44-7.41 (1H, m), 7.36 (2H, t, J = 7.5 Hz), 7.24-7.21 (6H, m), 6.70 (2H, s), 4.45-4.39 (1H, m), 3.48 (3H, s), 3.47-3.43 (1H, m), 3.11 (1H, dd, J_1 = 14.0 Hz, J_2 = 11.1 Hz), 2.44 (6H, s), 0.97 (9H, s), 0.18 (6H, s); $^{13}C\{^1H\}$ NMR (~101 MHz, $CDCl_3$): δ_C 172.0, 163.7, 153.3, 149.3, 147.8, 144.9, 141.5, 137.8, 137.0, 130.0, 128.2, 127.8, 126.6, 126.0, 124.4, 122.2, 121.2, 52.2, 51.9, 31.2, 25.6, 21.5, 18.1, -4.4; HRMS (ESI): *m/z* $[M+H]^+$ calcd for $C_{36}H_{43}N_2O_4Si$: 595.2992; found: 595.3003. The HPLC of compound **7k**-(DL) was determined by using the Daicel Chiralpak IA column, hexane/*i*-PrOH 95:05, flow rate 1.0 mL/min, UV detection at 254 nm, t_D = 7.51 min, t_L = 8.58 min.

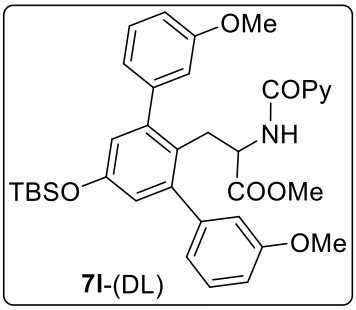


Methyl (*R*)-3-(5'-((tert-butyldimethylsilyl)oxy)-3,3''-dimethyl-[1,1':3',1''-terphenyl]-2'-yl)-2-(picolinamido)propanoate (7k-(D)): The compound **7k**-(D) was obtained from procedure D after purification by column chromatography on silica gel (EtOAc:hexanes = 30:70) as a colourless solid (50 mg, 56%, 0.15 mmol scale); R_f (EtOAc/hexanes = 30:70) 0.6; mp: 172-174 °C; IR (DCM): 3379, 2953, 1743, 1513 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ_H 8.58 (1H, d, J = 4.2 Hz), 8.05 (1H, d, J = 7.8 Hz), 7.82-7.76 (1H, m), 7.44-7.41 (1H, m), 7.36 (2H, t, J = 7.6 Hz), 7.24-7.21 (6H, m), 6.70 (2H, s), 4.45-4.39 (1H, m), 3.48 (3H, s), 3.47-3.42 (1H, m), 3.10 (1H, dd, J_1 = 14.0 Hz, J_2 = 11.0 Hz), 2.44 (6H, s), 0.97 (9H, s), 0.18 (6H, s); $^{13}C\{^1H\}$ NMR (~101 MHz, $CDCl_3$): δ_C 172.0, 163.7, 153.3, 149.3, 147.8, 144.9, 141.5, 137.8, 137.0, 130.0, 128.2, 127.8, 126.6, 126.0, 124.4, 122.2, 121.2, 52.2, 51.9, 31.2, 25.6, 21.5, 18.1, -4.4; HRMS (ESI): *m/z* $[M+H]^+$ calcd for $C_{36}H_{43}N_2O_4Si$: 595.2992; found: 595.3001. $[\alpha]^{25}_D$ = 44.9 (c = 0.02 g/mL, $CHCl_3$). The enantiomeric ratio (er 96:4) compound **7k**-(D) was determined by using the Daicel Chiralpak IA column, hexane/*i*-PrOH 95:05, flow rate 1.0 mL/min, UV detection at 254 nm, t_D = 7.46 min, t_L = 8.58 min.

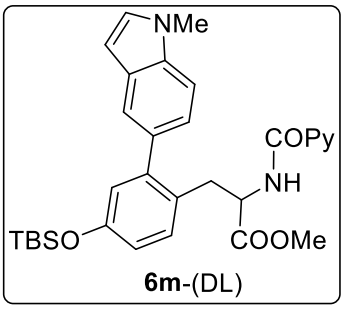


Methyl (*S*)-3-(5'-((tert-butyldimethylsilyl)oxy)-3,3''-dimethyl-[1,1':3',1''-terphenyl]-2'-yl)-2-(picolinamido)propanoate (7k-(L)): The compound **7k**-(L) was obtained from procedure D after purification by column chromatography on silica gel (EtOAc:hexanes = 30:70) as a colourless solid (63 mg, 71%, 0.15 mmol scale); R_f (EtOAc/hexanes = 30:70) 0.6; mp: 171-173 °C; IR (DCM): 3387, 2930, 1744, 1513 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ_H 8.58 (1H, d, J = 4.7 Hz), 8.05 (1H, d, J = 7.8 Hz), 7.82-7.76 (2H, m), 7.44-7.41 (1H, m), 7.36 (2H, t, J = 7.6 Hz), 7.24-7.21 (6H, m), 6.70 (2H, s), 4.45-4.39 (1H, m), 3.48 (3H, s), 3.47-3.43 (1H, m), 3.10 (1H, dd, J_1 = 14.0 Hz, J_2 = 11.0 Hz), 2.44 (6H, s), 0.97 (9H, s), 0.18 (6H, s); $^{13}C\{^1H\}$ NMR (~101 MHz, $CDCl_3$): δ_C 172.1, 163.8, 153.4, 149.4, 147.9, 145.0, 141.6, 137.9, 137.1, 130.1, 128.2, 127.9, 126.7, 126.1, 124.5, 122.3, 121.2, 52.3, 52.0, 31.3, 25.7, 21.6, 18.2, -4.4; HRMS (ESI): *m/z* $[M+H]^+$ calcd for $C_{36}H_{43}N_2O_4Si$: 595.2992; found: 595.2981. $[\alpha]^{25}_D$ = -40.9 (c = 0.02 g/mL, $CHCl_3$). The enantiomeric ratio (er 98:2) compound **7k**-(L) was determined by using the Daicel Chiralpak IA column, hexane/*i*-PrOH 95:05, flow rate 1.0 mL/min, UV detection at 254 nm, t_D = 7.50 min, t_L = 8.57 min.

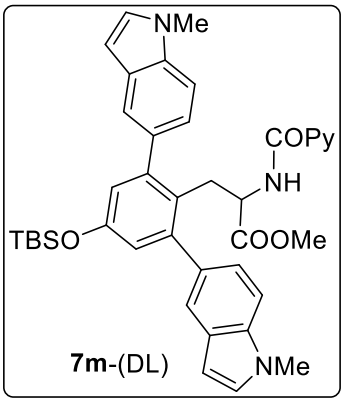


Methyl 3-(5'-((tert-butyldimethylsilyl)oxy)-3,3''-dimethoxy-[1,1':3',1''-terphenyl]-2'-yl)-2-(picolinamido)propanoate (7l-(DL)): 

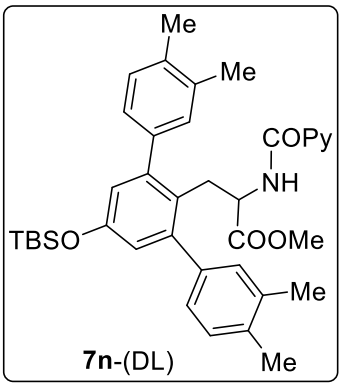
The compound **7l-(DL)** was obtained from procedure D after purification by column chromatography on silica gel (EtOAc:hexanes = 30:70) as a colourless solid (50 mg, 55%, 0.15 mmol scale); R_f (EtOAc/hexanes = 30:70) 0.4; mp: 162-164 ^oC; IR (DCM): 3379, 2953, 1743, 1513 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ_H 8.58 (1H, d, J = 4.3 Hz), 8.03 (1H, d, J = 7.8 Hz), 7.81-7.76 (2H, m), 7.43-7.35 (3H, m), 7.00-6.94 (6H, m), 6.70 (2H, s), 4.47-4.41 (1H, m), 3.86 (6H, s), 3.48 (3H, s), 3.42 (1H, dd, J_1 = 14.3 Hz, J_2 = 4.4 Hz), 3.13 (1H, dd, J_1 = 14.2 Hz, J_2 = 11.0 Hz), 0.95 (9H, s), 0.16 (6H, s); $^{13}C\{^1H\}$ NMR (~101 MHz, $CDCl_3$): δ_C 172.0, 163.9, 159.5, 153.4, 149.3, 148.0, 144.7, 142.9, 137.0, 129.4, 126.1, 124.5, 122.2, 122.0, 121.2, 115.3, 112.7, 55.3, 52.3, 52.0, 31.3, 25.6, 18.1, -4.4; HRMS (ESI): *m/z* $[M+H]^+$ calcd for $C_{36}H_{43}N_2O_6Si$: 627.2890; found: 627.2899.

Methyl 3-(4-((tert-butyldimethylsilyl)oxy)-2-(1-methyl-1H-indol-5-yl)phenyl)-2-(picolinamido)propanoate (6m-(DL)): 

The compound **6m-(DL)** was obtained from procedure D after purification by column chromatography on silica gel (EtOAc:hexanes = 30:70) as a brown coloured solid (16 mg, 29%, 0.10 mmol scale); R_f (EtOAc/hexanes = 30:70) 0.4; mp: 70-72 ^oC; IR (DCM): 3380, 2952, 1743, 1512 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ_H 8.57-8.56 (1H, m), 8.17 (1H, d, J = 8.2 Hz), 8.05 (1H, d, J = 7.8 Hz), 7.80 (1H, td, J_1 = 7.7 Hz, J_2 = 1.5 Hz), 7.53 (1H, d, J = 1.0 Hz), 7.44-7.41 (1H, m), 7.34 (1H, d, J = 8.4 Hz), 7.22-7.16 (2H, m), 7.10 (1H, d, J = 3.1 Hz), 6.79-6.76 (2H, m), 6.46 (1H, d, J = 3.0 Hz), 4.84-4.78 (1H, m), 3.84 (3H, s), 3.59 (3H, s), 3.31 (1H, dd, J_1 = 14.2 Hz, J_2 = 5.9 Hz), 3.18 (1H, dd, J_1 = 14.2 Hz, J_2 = 8.4 Hz), 0.97 (9H, s), 0.18 (6H, s); $^{13}C\{^1H\}$ NMR (~101 MHz, $CDCl_3$): δ_C 172.2, 163.9, 154.0, 149.3, 148.1, 145.2, 137.1, 135.8, 132.3, 130.5, 129.3, 128.4, 126.9, 126.1, 123.2, 122.5, 122.2, 121.5, 118.8, 108.8, 101.1, 53.6, 52.2, 34.3, 33.0, 25.7, 18.2, -4.4; HRMS (ESI): *m/z* $[M+H]^+$ calcd for $C_{31}H_{38}N_3O_4Si$: 544.2632; found: 544.2640.

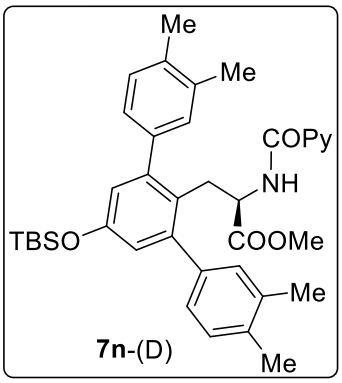
Methyl 3-(4-((tert-butyldimethylsilyl)oxy)-2,6-bis(1-methyl-1H-indol-5-yl)phenyl)-2-(picolinamido)propanoate (7m-(DL)): 

The compound **7m**-(DL) was obtained from procedure D after purification by column chromatography on silica gel (EtOAc:hexanes = 30:70) as a brown coloured solid (12 mg, 18%, 0.1 mmol scale); R_f (EtOAc/hexanes = 30:70) 0.3; mp: 198-200 ^{o}C; IR (DCM): 3374, 2928, 1743, 1514 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 8.60-8.58 (1H, m), 8.03 (1H, d, J = 7.8 Hz), 7.80 (1H, td, J_1 = 7.7 Hz, J_2 = 1.7 Hz), 7.72 (1H, d, J = 8.5 Hz), 7.67 (2H, s), 7.44-7.40 (3H, m), 7.32 (2H, dd, J_1 = 8.4 Hz, J_2 = 1.5 Hz), 7.12 (2H, d, J = 3.0 Hz), 6.76 (2H, s), 6.54 (2H, d, J = 2.7 Hz), 4.42-4.36 (1H, m), 3.87 (6H, s), 3.57 (1H, dd, J_1 = 14.1 Hz, J_2 = 4.3 Hz), 3.30 (3H, s), 3.25 (1H, dd, J_1 = 14.1 Hz, J_2 = 11.0 Hz), 0.95 (9H, s), 0.16 (3H, s), 0.16 (3H, s); ^{13}C{^{1}H} NMR (~101 MHz, $CDCl_3$): δ_C 172.1, 163.9, 153.1, 149.5, 147.8, 145.8, 137.0, 135.9, 133.1, 129.2, 128.5, 125.9, 125.4, 123.6, 122.2, 121.7, 121.6, 108.9, 101.2, 52.4, 51.8, 33.0, 31.2, 25.7, 18.2, -4.4; HRMS (ESI): *m/z* [M+H]$^{+}$ calcd for $C_{40}H_{45}N_4O_4Si$: 673.3210; found: 673.3220.

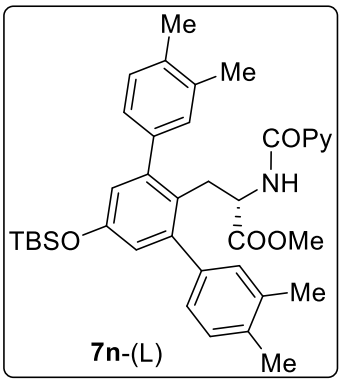
Methyl 3-(5'-((tert-butyldimethylsilyl)oxy)-3,3'',4,4''-tetramethyl-[1,1':3',1''-terphenyl]-2'-yl)-2-(picolinamido)propanoate (7n-(DL)): 

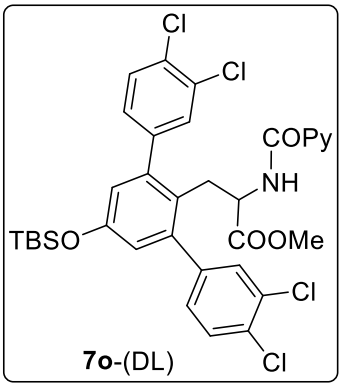
The compound **7n**-(DL) was obtained from procedure D after purification by column chromatography on silica gel (EtOAc:hexanes = 30:70) as a colourless solid (70 mg, 75%, 0.15 mmol scale); R_f (EtOAc/hexanes = 30:70) 0.6; mp: 124-126 ^{o}C; IR (DCM): 3387, 2951, 1743, 1510 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 8.55 (1H, d, J = 4.6 Hz), 8.01 (1H, d, J = 7.8 Hz), 7.78 (1H, td, J_1 = 7.6 Hz, J_2 = 1.5 Hz), 7.70 (1H, d, J = 8.6 Hz), 7.41-7.38 (1H, m), 7.19-7.09 (6H, m), 6.63 (2H, s), 4.38-4.33 (1H, m), 3.43 (3H, s), 3.46-3.41 (1H, m), 3.09 (1H, dd, J_1 = 14.2 Hz, J_2 = 10.9 Hz), 2.32 (6H, s), 2.30 (6H, s), 0.92 (9H, s), 0.12 (6H, s); ^{13}C{^{1}H} NMR (~101 MHz, $CDCl_3$): δ_C 172.1, 163.8, 153.3, 149.4, 147.8, 144.8, 139.2, 137.0, 136.3, 135.2, 130.5, 129.5, 126.9, 126.0, 124.6, 122.2, 121.1, 52.2, 51.9, 31.1, 25.6, 19.9, 19.5, 18.1, -4.5; HRMS (ESI): *m/z* [M+H]$^{+}$ calcd for $C_{38}H_{47}N_2O_4Si$: 623.3305; found: 623.3323. The HPLC of compound **7n**-(DL) was determined by using the Daicel Chiralpak IA column, hexane/*i*-PrOH 90:10, flow rate 1.0 mL/min, UV detection at 254 nm, t_D = 6.23 min, t_L = 7.22 min.

Methyl (*R*)-3-(5'-((tert-butyldimethylsilyl)oxy)-3,3'',4,4''-tetramethyl-[1,1':3',1''-terphenyl]-2'-yl)-2-(picolinamido)propanoate (7n-(D)): The compound **7n**-(D) was obtained from procedure D after purification by column chromatography on silica gel (EtOAc:hexanes = 30:70) as a colourless solid (70 mg, 75%, 0.15 mmol scale); R_f (EtOAc/hexanes = 30:70) 0.6; mp: 124-126 ºC; IR (DCM): 3387, 2951, 1744, 1511 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ_H 8.59 (1H, d, J = 4.7 Hz), 8.05 (1H, d, J = 7.8 Hz), 7.81 (1H, td, J_1 = 7.7 Hz, J_2 = 1.6 Hz), 7.75 (1H, d, J = 8.6 Hz), 7.45-7.41 (1H, m), 7.23-7.16 (6H, m), 6.68 (2H, s), 4.43-4.37 (1H, m), 3.49 (3H, s), 3.50-3.46 (1H, m), 3.14 (1H, dd, J_1 = 14.0 Hz, J_2 = 11.1 Hz), 2.36 (6H, s), 2.34 (6H, s), 0.96 (9H, s), 0.17 (6H, s); $^{13}C\{^1H\}$ NMR (~101 MHz, $CDCl_3$): δ_C 172.1, 163.8, 153.3, 149.4, 147.8, 144.8, 139.2, 137.0, 136.3, 135.2, 130.5, 129.5, 126.9, 126.0, 124.6, 122.2, 121.1, 52.2, 51.9, 31.1, 25.6, 19.8, 19.5, 18.1, -4.5; HRMS (ESI): *m/z* $[M+H]^+$ calcd for $C_{38}H_{47}N_2O_4Si$: 623.3305; found: 623.3316. $[\alpha]^{25}_D$ = 29.9 (c = 0.02 g/mL, DCM). The enantiomeric ratio (er 98:2) compound **7n**-(D) was determined by using the Daicel Chiralpak IA column, hexane/*i*-PrOH 90:10, flow rate 1.0 mL/min, UV detection at 254 nm, t_D = 6.19 min, t_L = 7.23 min.



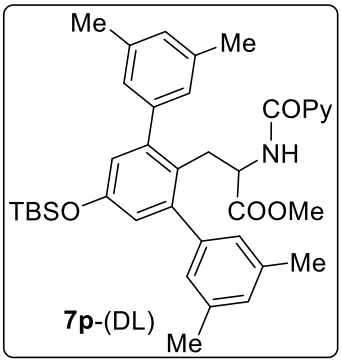
Methyl (*S*)-3-(5'-((tert-butyldimethylsilyl)oxy)-3,3'',4,4''-tetramethyl-[1,1':3',1''-terphenyl]-2'-yl)-2-(picolinamido)propanoate (7n-(L)): The compound **7n**-(L) was obtained from procedure D after purification by column chromatography on silica gel (EtOAc:hexanes = 30:70) as a colourless solid (68 mg, 73%, 0.15 mmol scale); R_f (EtOAc/hexanes = 30:70) 0.6; mp: 125-127 ºC; IR (DCM): 3386, 2931, 1744, 1510 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ_H 8.59 (1H, d, J = 4.5 Hz), 8.05 (1H, d, J = 7.8 Hz), 7.81 (1H, td, J_1 = 7.7 Hz, J_2 = 1.4 Hz), 7.76 (1H, d, J = 8.6 Hz), 7.45-7.42 (1H, m), 7.23-7.14 (6H, m), 6.69 (2H, s), 4.44-4.38 (1H, m), 3.50 (3H, s), 3.51-3.46 (1H, m), 3.14 (1H, dd, J_1 = 14.2 Hz, J_2 = 11.0 Hz), 2.36 (6H, s), 2.35 (6H, s), 0.96 (9H, s), 0.17 (6H, s); $^{13}C\{^1H\}$ NMR (~101 MHz, $CDCl_3$): δ_C 172.1, 163.8, 153.3, 149.4, 147.8, 144.8, 139.2, 137.0, 136.3, 135.2, 130.5, 129.5, 126.9, 126.0, 124.6, 122.2, 121.1, 52.2, 51.9, 31.1, 25.6, 19.9, 19.5, 18.1, -4.5; HRMS (ESI): *m/z* $[M+H]^+$ calcd for $C_{38}H_{47}N_2O_4Si$: 623.3305; found: 623.3303. $[\alpha]^{25}_D$ = -31.9 (c = 0.02 g/mL, DCM). The enantiomeric ratio (er 96:4) compound **7n**-(L) was determined by using the Daicel Chiralpak IA column, hexane/*i*-PrOH 90:10, flow rate 1.0 mL/min, UV detection at 254 nm, t_D = 6.17 min, t_L = 7.18 min.

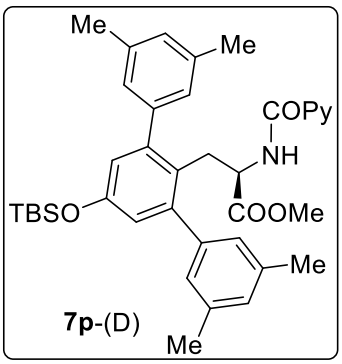




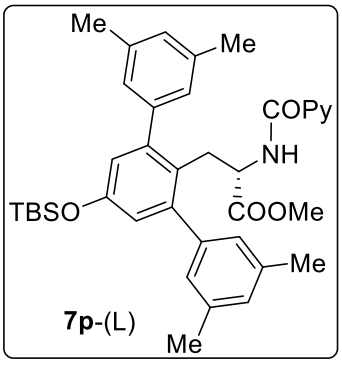
Methyl 3-(5'-((tert-butyldimethylsilyl)oxy)-3,3'',4,4''-tetrachloro-[1,1':3',1''-terphenyl]-2'-yl)-2-(picolinamido)propanoate (7o-(DL)): The compound **7o**-(DL) was obtained from procedure D after purification by column chromatography on silica gel (EtOAc:hexanes = 30:70) as a colourless solid (50 mg, 48%, 0.15 mmol scale); R_f (EtOAc/hexanes = 30:70) 0.55; mp: 184-186 ^{o}C; IR (DCM): 3383, 2930, 1743, 1512 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 8.61 (1H, d, J = 4.6 Hz), 8.00 (1H, d, J = 7.8 Hz), 7.82-7.76 (2H, m), 7.51-7.46 (4H, m), 7.47-7.42 (1H, m), 7.21 (2H, dd, J_1 = 8.2 Hz, J_2 = 1.7 Hz), 6.62 (2H, s), 4.45 (1H, td, J_1 = 10.8 Hz, J_2 = 3.7 Hz), 3.52 (3H, s), 3.34 (1H, dd, J_1 = 14.4 Hz, J_2 = 3.8 Hz), 2.97 (1H, dd, J_1 = 14.4 Hz, J_2 = 11.1 Hz), 0.93 (9H, s), 0.14 (3H, s), 0.13 (3H, s); ^{13}C{^{1}H} NMR (~101 MHz, $CDCl_3$): δ_C 171.5, 163.7, 153.8, 148.9, 148.3, 142.7, 141.2, 137.2, 132.5, 131.7, 131.3, 130.4, 129.1, 126.3, 124.4, 122.2, 121.8, 52.4, 52.0, 25.6, 31.6, 18.1, -4.4; HRMS (ESI): *m/z* [M+H]$^{+}$ calcd for $C_{34}H_{35}Cl_4N_2O_4Si$: 703.1120; found: 703.1123.

Methyl 3-(5'-((tert-butyldimethylsilyl)oxy)-3,3'',5,5''-tetramethyl-[1,1':3',1''-terphenyl]-2'-yl)-2-(picolinamido)propanoate (7p-(DL)): The compound **7p**-(DL) was obtained from procedure D after purification by column chromatography on silica gel (EtOAc:hexanes = 30:70) as a colourless solid (80 mg, 86%, 0.15 mmol scale); R_f (EtOAc/hexanes = 30:70) 0.7; mp: 136-138 ^{o}C; IR (DCM): 3388, 2929, 1744, 1513 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 8.59 (1H, d, J = 4.5 Hz), 8.07 (1H, d, J = 7.8 Hz), 7.82-7.76 (2H, m), 7.43 (1H, t, J = 6.0 Hz), 7.04 (6H, s), 6.69 (2H, s), 4.47-4.41 (1H, m), 3.50 (3H, s), 3.50-3.46 (1H, m), 3.14-3.08 (1H, m), 2.40 (12H, s), 0.97 (9H, s), 0.18 (6H, s); ^{13}C{^{1}H} NMR (~101 MHz, $CDCl_3$): δ_C 172.2, 163.8, 153.3, 149.6, 148.0, 145.0, 141.7, 137.7, 137.0, 128.7, 127.3, 126.0, 124.5, 122.3, 121.1, 52.3, 52.0, 31.4, 25.7, 21.4, 18.1, -4.4; HRMS (ESI): *m/z* [M+H]$^{+}$ calcd for $C_{38}H_{47}N_2O_4Si$: 623.3305; found: 623.3294.

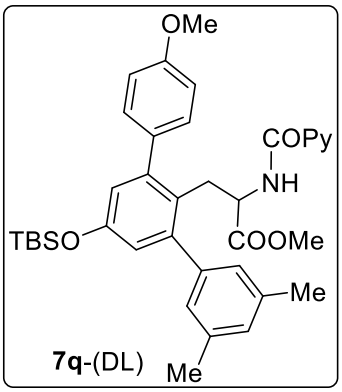


Methyl (*R*)-3-(5'-((tert-butyldimethylsilyl)oxy)-3,3'',5,5''-tetramethyl-[1,1':3',1''-terphenyl]-2'-yl)-2-(picolinamido)propanoate (7p-(D): 

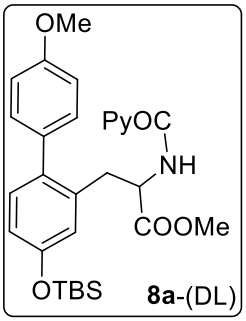
The compound **7p**-(D) was obtained from procedure D after purification by column chromatography on silica gel (EtOAc:hexanes = 30:70) as a colourless solid (57 mg, 61%, 0.15 mmol scale); R_f (EtOAc/hexanes = 30:70) 0.7; mp: 137-139 ºC; IR (DCM): 3386, 2929, 1743, 1514 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ_H 8.58 (1H, dd, J_1 = 4.7 Hz, J_2 = 0.6 Hz), 8.06 (1H, d, J = 7.8 Hz), 7.81 (1H, td, J_1 = 7.7 Hz, J_2 = 1.7 Hz), 7.76 (1H, d, J = 8.8 Hz), 7.44-7.41 (1H, m), 7.03 (6H, s), 6.67 (2H, s), 4.45-4.39 (1H, m), 3.49 (3H, s), 3.48-3.44 (1H, m), 3.09 (1H, dd, J_1 = 14.2 Hz, J_2 = 11.0 Hz), 2.39 (12H, s), 0.96 (9H, s), 0.17 (6H, s); $^{13}C\{^1H\}$ NMR (~101 MHz, $CDCl_3$): δ_C 172.2, 163.8, 153.3, 149.6, 148.0, 145.0, 141.7, 137.7, 137.0, 128.7, 127.3, 126.0, 124.5, 122.3, 121.1, 52.3, 52.0, 31.4, 25.7, 21.4, 18.1, -4.4; HRMS (ESI): *m/z* $[M+H]^+$ calcd for $C_{38}H_{47}N_2O_4Si$: 623.3305; found: 623.3296. $[\alpha]^{25}_D$ = 39.9 (c = 0.02 g/mL, $CHCl_3$).

Methyl (*S*)-3-(5'-((tert-butyldimethylsilyl)oxy)-3,3'',5,5''-tetramethyl-[1,1':3',1''-terphenyl]-2'-yl)-2-(picolinamido)propanoate (7p-(L)): 

The compound **7p**-(L) was obtained from procedure D after purification by column chromatography on silica gel (EtOAc:hexanes = 30:70) as a colourless solid (63 mg, 68%, 0.15 mmol scale); R_f (EtOAc/hexanes = 30:70) 0.7; mp: 135-137 ºC; IR (DCM): 3389, 2928, 1744, 1513 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ_H 8.58 (1H, d, J = 4.7 Hz), 8.07 (1H, d, J = 7.8 Hz), 7.83-7.77 (2H, m), 7.44-7.41 (1H, m), 7.05 (6H, s), 6.69 (2H, s), 4.48-4.42 (1H, m), 3.51 (3H, s), 3.50-3.47 (1H, m), 3.11 (1H, dd, J_1 = 14.2 Hz, J_2 = 11.0 Hz), 2.40 (12H, s), 0.98 (9H, s), 0.19 (6H, s); $^{13}C\{^1H\}$ NMR (~101 MHz, $CDCl_3$): δ_C 172.1, 163.7, 153.2, 149.5, 147.9, 144.9, 141.6, 137.6, 137.0, 128.6, 127.2, 125.9, 124.4, 122.2, 121.0, 52.2, 51.9, 31.3, 25.6, 21.4, 18.0, -4.5; $[\alpha]^{25}_D$ = -38.9 (c = 0.02 g/mL, $CHCl_3$). HRMS (ESI): *m/z* $[M+H]^+$ calcd for $C_{38}H_{47}N_2O_4Si$: 623.3305; found: 623.3318.

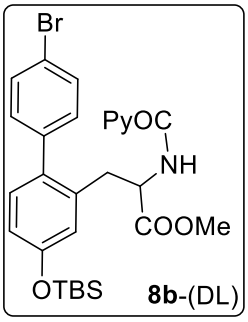
Methyl 3-(5'-((tert-butyldimethylsilyl)oxy)-4''-methoxy-3,5-dimethyl-[1,1':3',1''-terphenyl]-2'-yl)-2-(picolinamido)propanoate (7q-(DL)): 

The compound **7q**-(DL) was obtained from procedure D after purification by column chromatography on silica gel (EtOAc:hexanes = 30:70) as a colourless semi solid (12 mg, 64%, 0.03 mmol scale); R_f (EtOAc/hexanes = 30:70) 0.5; IR (DCM): 3387, 2930, 1745, 1513 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ_H 8.58 (1H, d, J = 4.5 Hz), 8.04 (1H, d, J = 7.8 Hz), 7.80 (1H, td, J_1 = 7.7 Hz, J_2 = 1.6 Hz), 7.75 (1H, d, J = 8.8 Hz), 7.44-7.41 (1H, m), 7.36 (2H, d, J = 8.6 Hz), 7.02-6.98 (5H, m), 6.65 (2H, dd, J_1 = 10.9 Hz, J_2 = 2.6 Hz), 4.44-4.38 (1H, m), 3.89 (3H, s), 3.48 (3H, s), 3.43 (1H, dd, J_1 = 14.3 Hz, J_2 = 4.3 Hz), 3.08 (1H, dd, J_1 = 14.3 Hz, J_2 = 11.1 Hz), 2.38 (6H, s), 0.94 (9H, s), 0.15 (3H, s), 0.15 (3H, s); $^{13}C\{^1H\}$ NMR (~101 MHz, $CDCl_3$): δ_C 172.1, 163.8, 158.7, 153.3, 149.5, 147.9, 145.2, 144.3, 141.7, 137.7, 137.1, 134.1, 130.6, 128.7, 127.3, 126.1, 124.7, 122.3, 121.5, 121.0, 113.8, 55.3, 52.2, 52.01, 31.3, 25.6, 21.4, 18.4, -4.4; HRMS (ESI): *m/z* $[M+H]^+$ calcd for $C_{37}H_{45}N_2O_5Si$: 625.3098; found: 625.3084.

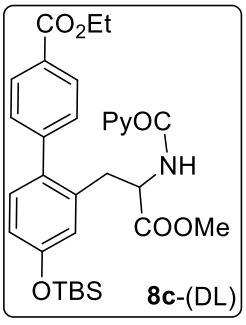
Methyl 3-(4-((tert-butyldimethylsilyl)oxy)-4'-methoxy-[1,1'-biphenyl]-2-yl)-2-(picolinamido)propanoate (8a-(DL)): 

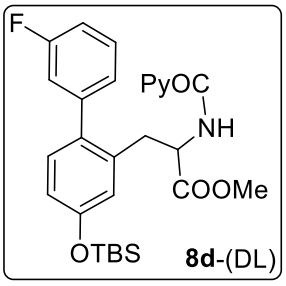
The compound **8a**-(DL) was obtained from procedure D after purification by column chromatography on silica gel (EtOAc:hexanes = 30:70) as a colourless solid (38 mg, 73%, 0.1 mmol scale); R_f (EtOAc/hexanes = 30:70) 0.4; mp: 118-120 ºC; IR (DCM): 3388, 2931, 1743, 1512 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ_H 8.55-8.53 (1H, m), 8.24 (1H, d, J = 8.3 Hz), 8.06 (1H, dt, J_1 = 7.8 Hz, J_2 = 0.9 Hz), 7.79 (1H, td, J_1 = 7.7 Hz, J_2 = 1.7 Hz), 7.42-7.39 (1H, m), 7.20 (2H, dt, J_1 = 8.7 Hz, J_2 = 2.9 Hz), 7.03 (1H, d, J = 8.2 Hz), 6.88 (2H, dt, J_1 = 8.7 Hz, J_2 = 2.9 Hz), 6.78 (1H, d, J = 2.5 Hz), 6.71 (1H, dd, J_1 = 8.3 Hz, J_2 = 2.5 Hz), 4.83-4.77 (1H, m), 3.82 (3H, s), 3.63 (3H, s), 3.32 (1H, dd, J_1 = 14.1 Hz, J_2 = 5.5 Hz), 3.07 (1H, dd, J_1 = 14.1 Hz, J_2 = 8.5 Hz), 0.95 (9H, s), 0.15 (3H, s), 0.14 (3H, s); $^{13}C\{^1H\}$ NMR (~101 MHz, $CDCl_3$): δ_C 172.0, 163.9, 158.4, 154.7, 149.2, 148.1, 137.2, 135.6, 135.1, 133.4, 131.6, 130.7, 126.3, 122.2, 121.2, 118.5, 113.6, 55.3, 53.2, 52.3, 35.1, 25.6, 18.1, -4.5; HRMS (ESI): *m/z* $[M+Na]^+$ calcd for $C_{29}H_{36}N_2NaO_5Si$: 543.2291; found: 543.2299.

Methyl 3-(4'-bromo-4-((tert-butyldimethylsilyl)oxy)-[1,1'-biphenyl]-2-yl)-2-(picolinamido)propanoate (8b-(DL)): The compound **8b**-(DL) was obtained from procedure D after purification by column chromatography on silica gel (EtOAc:hexanes = 30:70) as a yellow coloured semi solid (32 mg, 56%, 0.1 mmol scale); R_f (EtOAc/hexanes = 30:70) 0.6; IR (DCM): 3378, 2954, 1744, 1511 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ_H 8.55-8.53 (1H, m), 8.23 (1H, d, J = 8.4 Hz), 8.05 (1H, dt, J_1 = 7.8 Hz, J_2 = 1.0 Hz), 7.81 (1H, td, J_1 = 7.7 Hz, J_2 = 1.7 Hz), 7.43-7.40 (3H, m), 7.14 (2H, dt, J_1 = 8.4 Hz, J_2 = 2.4 Hz), 7.00 (1H, d, J = 8.3 Hz), 6.78 (1H, d, J = 2.5 Hz), 6.72 (1H, dd, J_1 = 8.2 Hz, J_2 = 2.5 Hz), 4.84-4.79 (1H, m), 3.64 (3H, s), 3.33 (1H, dd, J_1 = 14.1 Hz, J_2 = 5.4 Hz), 3.05 (1H, dd, J_1 = 14.1 Hz, J_2 = 8.2 Hz), 0.94 (9H, s), 0.15 (3H, s), 0.14 (3H, s); $^{13}C\{^1H\}$ NMR (~101 MHz, $CDCl_3$): δ_C 171.7, 163.8, 155.1, 149.2, 148.1, 140.0, 137.2, 134.9, 134.6, 131.4, 131.3, 131.3, 126.3, 122.3, 121.5, 121.0, 118.7, 53.2, 52.4, 35.0, 25.6, 18.1, -4.5; HRMS (ESI): *m/z* $[M+Na]^+$ calcd for $C_{28}H_{33}BrN_2NaO_4Si$: 591.1291; found: 591.1282.

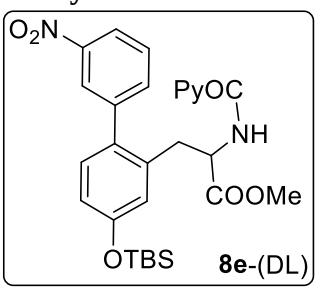


Ethyl 4'-((tert-butyldimethylsilyl)oxy)-2'-(3-methoxy-3-oxo-2-(picolinamido)propyl)-[1,1'-biphenyl]-4-carboxylate (8c-(DL)): The compound **8c**-(DL) was obtained from procedure D after purification by column chromatography on silica gel (EtOAc:hexanes = 30:70) as a yellow coloured semi solid (32 mg, 52%, 0.1 mmol scale); R_f (EtOAc/hexanes = 30:70) 0.3; IR (DCM): 3375, 2954, 1714, 1513 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ_H 8.56-8.55 (1H, m), 8.24 (1H, d, J = 8.4 Hz), 8.04 (1H, dt, J_1 = 7.8 Hz, J_2 = 1.1 Hz), 8.01 (2H, dt, J_1 = 8.4 Hz, J_2 = 1.8 Hz), 7.81 (1H, td, J_1 = 7.7 Hz, J_2 = 1.7 Hz), 7.45-7.41 (1H, m), 7.35 (2H, dd, J_1 = 8.4 Hz, J_2 = 1.7 Hz), 7.05 (1H, d, J = 8.3 Hz), 6.82 (1H, d, J = 2.4 Hz), 6.76 (1H, dd, J_1 = 8.3 Hz, J_2 = 2.5 Hz), 4.85-4.79 (1H, m), 4.41 (2H, q, J = 7.1 Hz), 3.64 (3H, s), 3.35 (1H, dd, J_1 = 14.1 Hz, J_2 = 5.4 Hz), 3.09 (1H, dd, J_1 = 14.2 Hz, J_2 = 8.2 Hz), 1.43 (3H, t, J = 7.1 Hz), 0.96 (9H, s), 0.17 (3H, s), 0.16 (3H, s); HRMS (ESI): *m/z* $[M+H]^+$ calcd for $C_{31}H_{39}N_2O_6Si$: 563.2577; found: 563.2581. $^{13}C\{^1H\}$ NMR (~101 MHz, $CDCl_3$): δ_C 171.7, 166.5, 163.8, 155.3, 149.1, 148.1, 145.9, 137.2, 134.9, 134.9, 131.3, 129.7, 129.5, 128.8, 126.3, 122.3, 121.6, 118.8, 60.9, 53.2, 52.4, 35.0, 25.6, 18.1, 14.4, -4.4;

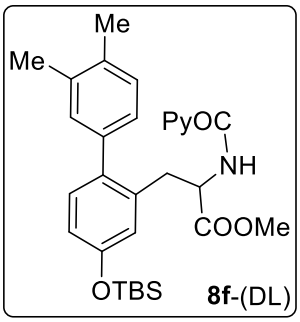


Methyl 3-(4-((tert-butyldimethylsilyl)oxy)-3'-fluoro-[1,1'-biphenyl]-2-yl)-2-(picolinamido)propanoate (8d-(DL)): 

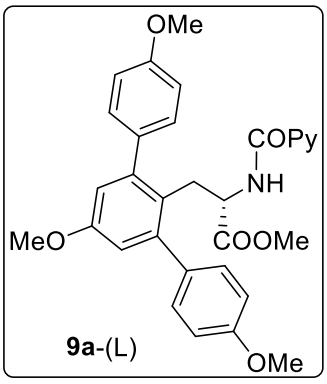
The compound **8d**-(DL) was obtained from procedure D after purification by column chromatography on silica gel (EtOAc:hexanes = 30:70) as a yellow coloured semi solid (32 mg, 64%, 0.1 mmol scale); R_f(EtOAc/hexanes = 30:70) 0.6; IR (DCM): 3385, 2930, 1745, 1512 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ_H 8.57 (1H, d, J = 4.7 Hz), 8.25 (1H, d, J = 8.4 Hz), 8.08 (1H, d, J = 7.8 Hz), 7.82 (1H, td, J_1 = 7.7 Hz, J_2 = 1.6 Hz), 7.45-7.42 (1H, m), 7.34-7.30 (1H, m), 7.07-6.99 (4H, m), 6.81 (1H, d, J = 2.4 Hz), 6.75 (1H, dd, J_1 = 8.3 Hz, J_2 = 2.4 Hz), 4.86-4.80 (1H, m), 3.66 (3H, s), 3.33 (1H, dd, J_1 = 14.1 Hz, J_2 = 5.4 Hz), 3.09 (1H, dd, J_1 = 14.1 Hz, J_2 = 8.4 Hz), 0.97 (9H, s), 0.18 (3H, s), 0.17 (3H, s); $^{13}C\{^1H\}$ NMR (~101 MHz, $CDCl_3$): δ_C 171.8, 163.8, 162.6 (d, J_{C-F} = 244.8 Hz), 155.2, 149.1, 148.2, 143.2 (d, J_{C-F} = 7.6 Hz), 137.2, 134.9, 134.7 (d, J_{C-F} = 1.8 Hz), 131.3, 129.5 (d, J_{C-F} = 2.6 Hz), 126.3, 125.5 (d, J_{C-F} = 2.6 Hz), 122.2, 121.4, 118.7, 116.8 (d, J_{C-F} = 20.8 Hz), 113.7 (d, J_{C-F} = 20.8 Hz), 53.3, 52.3, 35.0, 25.6, 18.1, -4.5; $^{19}F\{^1H\}$ NMR (~376 MHz, $CDCl_3$): δ_F = -113.2; HRMS (ESI): *m/z* $[M+Na]^+$ calcd for $C_{28}H_{33}FN_2NaO_4Si$: 531.2091; found: 531.2100.

Methyl 3-(4-((tert-butyldimethylsilyl)oxy)-3'-nitro-[1,1'-biphenyl]-2-yl)-2-(picolinamido)propanoate (8e-(DL)): 

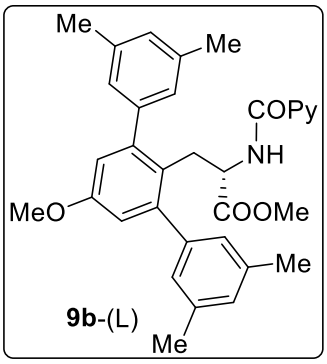
The compound **8e**-(DL) was obtained from procedure D after purification by column chromatography on silica gel (EtOAc:hexanes = 30:70) as a yellow coloured semi solid (30 mg, 52%, 0.1 mmol scale); R_f (EtOAc/hexanes = 30:70) 0.2; IR (DCM): 3375, 1743, 1508, 1264 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ_H 8.53 (1H, d, J = 4.6 Hz), 8.30 (1H, d, J = 8.2 Hz), 8.13-8.10 (2H, m), 8.01 (1H, d, J = 7.8 Hz), 7.82 (1H, t, J = 7.7 Hz), 7.63 (1H, d, J = 7.6 Hz), 7.51 (1H, t, J = 7.8 Hz), 7.45-7.42 (1H, m), 7.05 (1H, d, J = 8.3 Hz), 6.82 (1H, d, J = 2.4 Hz), 6.78 (1H, dd, J_1 = 8.3 Hz, J_2 = 2.4 Hz), 4.83-4.77 (1H, m), 3.65 (3H, s), 3.36 (1H, dd, J_1 = 14.2 Hz, J_2 = 5.4 Hz), 3.09 (1H, dd, J_1 = 14.2 Hz, J_2 = 7.8 Hz), 0.96 (9H, s), 0.18 (3H, s), 0.17 (3H, s); $^{13}C\{^1H\}$ NMR (~101 MHz, $CDCl_3$): δ_C 171.5, 163.6, 155.8, 148.9, 148.2, 148.0, 142.8, 137.3, 136.0, 135.0, 133.4, 131.5, 129.1, 126.5, 124.5, 122.2, 121.8, 119.0, 53.2, 52.4, 34.9, 25.6, 18.1, -4.4; HRMS (ESI): *m/z* $[M+Na]^+$ calcd for $C_{28}H_{33}N_3NaO_6Si$: 558.2036; found: 558.2026.

Methyl 3-(4-((tert-butyldimethylsilyl)oxy)-3',4'-dimethyl-[1,1'-biphenyl]-2-yl)-2-(picolinamido)propanoate (8f-DL): 

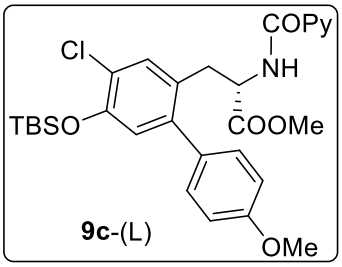
The compound **8f**-(DL) was obtained from procedure D after purification by column chromatography on silica gel (EtOAc:hexanes = 30:70) as a colourless solid (36 mg, 63%, 0.1 mmol scale); R_f (EtOAc/hexanes = 30:70) 0.6; mp: 80-82 ºC; IR (DCM): 3373, 2931, 1744, 1516 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ_H 8.54 (1H, d, J = 4.6 Hz), 8.22 (1H, d, J = 8.2 Hz), 8.07 (1H, d, J = 7.8 Hz), 7.79 (1H, td, J_1 = 7.7 Hz, J_2 = 1.3 Hz), 7.42-7.39 (1H, m), 7.10 (1H, d, J = 7.6 Hz), 7.04-6.99 (3H, m), 6.79 (1H, d, J = 2.4 Hz), 6.71 (1H, dd, J_1 = 8.3 Hz, J_2 = 2.4 Hz), 4.86-4.80 (1H, m), 3.63 (3H, s), 3.31 (1H, dd, J_1 = 14.1 Hz, J_2 = 5.5 Hz), 3.09 (1H, dd, J_1 = 14.1 Hz, J_2 = 8.4 Hz), 2.27 (3H, s), 2.23 (3H, s), 0.95 (9H, s), 0.15 (3H, s), 0.14 (3H, s); $^{13}C\{^1H\}$ NMR (~101 MHz, $CDCl_3$): δ_C 172.0, 163.9, 154.7, 149.3, 148.1, 138.6, 137.1, 136.3, 136.1, 134.9, 134.9, 131.4, 130.9, 129.4, 127.1, 126.2, 122.2, 121.0, 118.5, 53.3, 52.3, 34.9, 25.7, 19.8, 19.5, 18.1, -4.4; HRMS (ESI): *m/z* $[M+Na]^+$ calcd for $C_{30}H_{38}N_2NaO_4Si$: 541.2499; found: 541.2498.

Methyl (*S*)-2-(picolinamido)-3-(4,4'',5'-trimethoxy-[1,1':3',1''-terphenyl]-2'-yl)propanoate (9a-(L)): 

The compound **9a**-(L) was obtained from procedure D after purification by column chromatography on silica gel (EtOAc:hexanes = 30:70) as a colourless solid (36 mg, 69%, 0.1 mmol scale); R_f (EtOAc/hexanes = 30:70) 0.3; mp: 131-133 ºC; IR (DCM): 3379, 2952, 1742, 1510 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ_H 8.59-8.57 (1H, m), 8.04 (1H, dt, J_1 = 7.7 Hz, J_2 = 1.0 Hz), 7.82-7.77 (2H, m), 7.44-7.41 (1H, m), 7.33 (4H, d, J = 8.6 Hz), 6.99 (4H, d, J = 8.7 Hz), 6.72 (2H, s), 4.44-4.38 (1H, m), 3.89 (6H, s), 3.77 (3H, s), 3.48 (3H, s), 3.41 (1H, dd, J_1 = 14.3 Hz, J_2 = 4.2 Hz), 3.11 (1H, dd, J_1 = 14.3 Hz, J_2 = 11.0 Hz); $^{13}C\{^1H\}$ NMR (~101 MHz, $CDCl_3$): δ_C 172.0, 163.9, 158.8, 157.3, 149.3, 147.8, 144.5, 137.1, 134.1, 130.6, 126.2, 124.4, 122.2, 115.2, 113.8, 55.3, 52.2, 52.4, 52.0, 31.2; HRMS (ESI): *m/z* $[M+H]^+$ calcd for $C_{31}H_{31}N_2O_6$: 527.2182; found: 527.2189. $[\alpha]^{25}_D$ = -33.9 (c = 0.02 g/mL, $CHCl_3$). The HPLC of compound **9a**-(L) was determined by using the Daicel Chiralpak IC column, hexane/*i*-PrOH 50:50, flow rate 1.0 mL/min, UV detection at 254 nm, t_D = -, t_L = 14.44 min.

Methyl (*S*)-3-(5'-methoxy-3,3'',5,5''-tetramethyl-[1,1':3',1''-terphenyl]-2'-yl)-2-(picolinamido)propanoate (9b-(L)): 

The compound **9b**-(L) was obtained from procedure D after purification by column chromatography on silica gel (EtOAc:hexanes = 30:70) as a colourless semi solid (37 mg, 71%, 0.1 mmol scale); R_f (EtOAc/hexanes = 30:70) 0.6; IR (DCM): 3388, 2920, 1742, 1512 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ_H 8.58 (1H, d, J = 4.7 Hz), 8.07 (1H, d, J = 7.8 Hz), 7.81 (2H, dt, J_1 = 7.7 Hz, J_2 = 1.6 Hz), 7.44-7.41 (1H, m), 7.04 (6H, s), 6.73 (2H, s), 4.48-4.43 (1H, m), 3.78 (3H, s), 3.49 (3H, s), 3.48 (1H, dd, J_1 = 14.2 Hz, J_2 = 9.9 Hz), 3.10 (1H, dd, J_1 = 14.3 Hz, J_2 = 10.9 Hz), 2.39 (12H, s); $^{13}C\{^1H\}$ NMR (~101 MHz, $CDCl_3$): δ_C 172.2, 163.9, 157.3, 149.5, 148.0, 145.0, 141.7, 137.8, 137.1, 128.8, 127.3, 126.0, 123.9, 122.3, 115.0, 55.2, 52.5, 52.0, 31.4, 21.4; HRMS (ESI): *m/z* $[M+H]^+$ calcd for $C_{33}H_{35}N_2O_4$: 523.2597; found: 523.2597. $[\alpha]^{25}_D$ = -30.9 (c = 0.02 g/mL, $CHCl_3$). The HPLC of compound **9b**-(L) was determined by using the Daicel Chiralcel IC column, hexane/*i*-PrOH 80:20, flow rate 1.0 mL/min, UV detection at 254 nm, t_D = , t_L = 7.06 min.

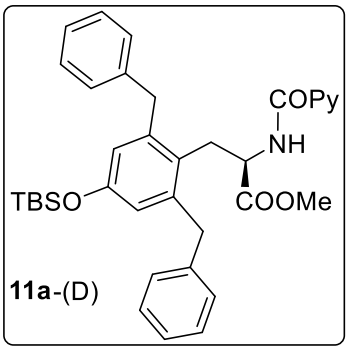
Methyl (*S*)-3-(5-((tert-butyldimethylsilyl)oxy)-4-chloro-4'-methoxy-[1,1'-biphenyl]-2-yl)-2-(picolinamido)propanoate (9c-(L)): 

The compound **9c**-(L) was obtained from procedure D after purification by column chromatography on silica gel (EtOAc:hexanes = 30:70) as a colourless semi solid (18 mg, 33%, 0.1 mmol scale); R_f (EtOAc/hexanes = 30:70) 0.4; IR (DCM): 3378, 2931, 1744, 1513 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ_H 8.57 (1H, d, J = 4.6 Hz), 8.21 (1H, d, J = 8.3 Hz), 8.07 (1H, d, J = 7.8 Hz), 7.83 (1H, t, J = 7.6 Hz), 7.45-7.42 (1H, m), 7.28 (1H, s), 7.19 (2H, d, J = 8.4 Hz), 6.88 (2H, d, J = 8.4 Hz), 6.72 (1H, s), 4.81-4.75 (1H, m), 3.84 (3H, s), 3.65 (3H, s), 3.27 (1H, dd, J_1 = 14.1 Hz, J_2 = 5.9 Hz), 3.08 (1H, dd, J_1 = 14.1 Hz, J_2 = 7.9 Hz), 1.01 (9H, s), 0.20 (6H, s); $^{13}C\{^1H\}$ NMR (~101 MHz, $CDCl_3$): δ_C 171.8, 163.8, 158.8, 150.0, 149.2, 148.1, 141.9, 137.1, 132.5, 131.5, 130.3, 127.9, 126.3, 124.2, 122.7, 122.2, 113.7, 55.3, 53.3, 52.3, 34.3, 25.6, 18.3, -4.3; HRMS (ESI): *m/z* $[M+H]^+$ calcd for $C_{29}H_{36}ClN_2O_5Si$: 555.2082; found: 555.2076. $[\alpha]^{25}_D$ = +11.3 (c = 0.03 g/mL, $CHCl_3$). The HPLC of compound **9c**-(L) was determined by using the Daicel Chiralcel IC column, hexane/*i*-PrOH 80:20, flow rate 1.0 mL/min, UV detection at 254 nm, t_D = -, t_L = 7.67 min.

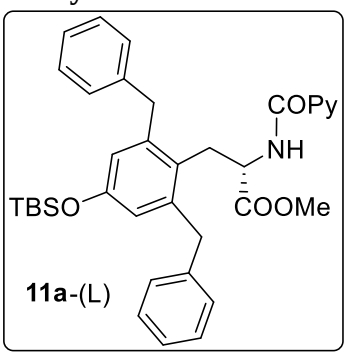
Methyl (*S*)-3-(5-((tert-butyldimethylsilyl)oxy)-4-chloro-3',5'-dimethyl-[1,1'-biphenyl]-2-yl)-2-(picolinamido)propanoate (9d-(L)): The compound **9d**-(L) was obtained from procedure D after purification by column chromatography on silica gel (EtOAc:hexanes = 30:70) as a colourless solid (31 mg, 56%, 0.1 mmol scale); R_f (EtOAc/hexanes = 30:70) 0.65; mp: 96-98 ^oC; IR (DCM): 3385, 2953, 1745, 1494 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ_H 8.59-8.58 (1H, m), 8.22 (1H, d, J = 8.4 Hz), 8.09 (1H, dt, J_1 = 7.8 Hz, J_2 = 1.0 Hz), 7.83 (1H, td, J_1 = 7.7 Hz, J_2 = 1.7 Hz), 7.46-7.42 (1H, m), 7.30 (1H, s), 6.97 (1H, s), 6.87 (2H, s), 6.73 (1H, s), 4.85-4.80 (1H, m), 3.66 (3H, s), 3.24 (1H, dd, J_1 = 14.2 Hz, J_2 = 5.9 Hz), 3.06 (1H, dd, J_1 = 14.1 Hz, J_2 = 7.9 Hz), 2.31 (6H, s), 1.02 (9H, s), 0.21 (6H, s); $^{13}C\{^1H\}$ NMR (~101 MHz, $CDCl_3$): δ_C 171.9, 163.8, 149.9, 149.2, 148.2, 142.6, 140.1, 137.8, 137.2, 131.3, 128.9, 127.7, 127.0, 126.3, 124.3, 122.3, 122.3, 53.4, 52.3, 34.2, 25.7, 21.3, 18.3, -4.3; HRMS (ESI): *m/z* $[M+H]^+$ calcd for $C_{30}H_{38}ClN_2O_4Si$: 553.2289; found: 553.2288. $[\alpha]^{25}_D$ = +3.33 (c = 0.03 g/mL, $CHCl_3$). The HPLC of compound **9d**-(L) was determined by using the Daicel Chiralcel IC column, hexane/*i*-PrOH 80:20, flow rate 1.0 mL/min, UV detection at 254 nm, t_D = -, t_L = 6.40 min.

Methyl 3-(2,6-dibenzyl-4-((tert-butyldimethylsilyl)oxy)phenyl)-2-(picolinamido)propanoate (11a-(DL)): The compound **11a**-(DL) was obtained from procedure E after purification by column chromatography on silica gel (EtOAc:hexanes = 30:70) as a colourless solid (34 mg, 57%, 0.1 mmol scale); R_f (EtOAc/hexanes = 30:70) 0.55; mp: 102-104 ^oC; IR (DCM): 3380, 2930, 1741, 1513 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ_H 8.60-8.56 (2H, m), 8.14 (1H, d, J = 7.8 Hz), 7.87-7.82 (1H, m), 7.47-7.44 (1H, m), 7.29-7.26 (4H, m), 7.20 (2H, t, J = 7.3 Hz), 7.12 (4H, d, J = 7.1 Hz), 6.46 (2H, s), 5.03 (1H, q, J = 8.2 Hz), 4.11 (4H, s), 3.71 (3H, s), 3.20-3.10 (2H, m), 0.90 (9H, s), 0.05 (6H, s); $^{13}C\{^1H\}$ NMR (~101 MHz, $CDCl_3$): δ_C 172.7, 163.9, 154.4, 149.3, 148.2, 141.4, 140.5, 137.3, 128.9, 128.4, 126.4, 126.2, 126.0, 122.3, 120.8, 52.8, 52.4, 39.1, 31.7, 25.7, 18.2, -4.4; HRMS (ESI): *m/z* $[M+H]^+$ calcd for $C_{36}H_{43}N_2O_4Si$: 595.2992; found: 595.3000. The HPLC of compound **11a**-(DL) was determined by using the Daicel Chiralcel OD column, hexane/*i*-PrOH 50:50, flow rate 1.0 mL/min, UV detection at 254 nm, t_D = 6.01 min, t_L = 8.39 min.

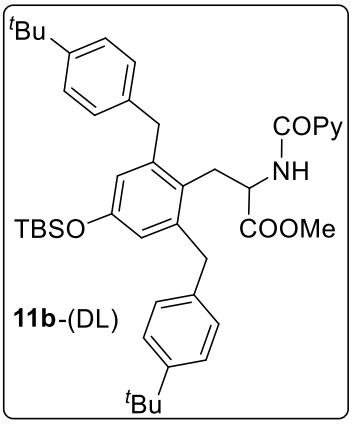
Methyl (*R*)-3-(2,6-dibenzyl-4-((tert-butyldimethylsilyl)oxy)phenyl)-2-(picolinamido)propanoate (11a-(D)): The compound **11a**-(D) was obtained from procedure E after purification by column chromatography on silica gel (EtOAc:hexanes = 30:70) as a colourless solid (45 mg, 76%, 0.1 mmol scale); R_f (EtOAc/hexanes = 30:70) 0.55; mp: 103-105 °C; IR (DCM): 3381, 2953, 1741, 1513 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ_H 8.61-8.59 (1H, m), 8.56 (1H, d, J = 8.5 Hz), 8.14 (1H, dt, J_1 = 7.8 Hz, J_2 = 0.9 Hz), 7.85 (1H, td, J_1 = 7.7 Hz, J_2 = 1.7 Hz), 7.47-7.43 (1H, m), 7.29-7.26 (4H, m), 7.22-7.18 (2H, m), 7.13 (4H, d, J = 7.0 Hz), 6.46 (2H, s), 5.03 (1H, q, J = 8.1 Hz), 4.11 (4H, s), 3.71 (3H, s), 3.21-3.10 (2H, m), 0.89 (9H, s), 0.05 (6H, s); $^{13}C\{^1H\}$ NMR (~101 MHz, $CDCl_3$): δ_C 172.6, 163.9, 154.4, 149.3, 148.2, 141.4, 140.5, 137.3, 128.9, 128.4, 126.3, 126.2, 126.0, 122.3, 120.8, 52.8, 52.4, 39.1, 31.7, 25.7, 18.2, -4.5; HRMS (ESI): *m/z* $[M+H]^+$ calcd for $C_{36}H_{43}N_2O_4Si$: 595.2992; found: 595.3011. $[\alpha]^{25}_D$ = +6.6 (c = 0.03 g/mL, $CHCl_3$). The enantiomeric ratio (er 97:3) of compound **11a**-(D) was determined by using the Daicel Chiralcel OD column, hexane/*i*-PrOH 50:50, flow rate 1.0 mL/min, UV detection at 254 nm, t_D = 5.98 min, t_L = 8.31 min.



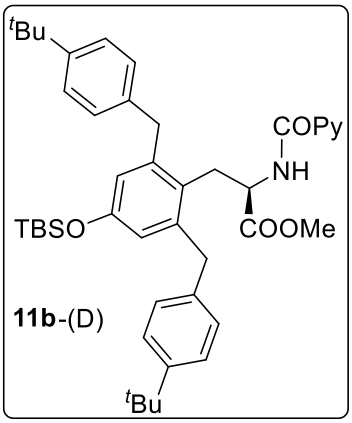
Methyl (*S*)-3-(2,6-dibenzyl-4-((tert-butyldimethylsilyl)oxy)phenyl)-2-(picolinamido)propanoate (11a-(L)): The compound **11a**-(L) was obtained from procedure E after purification by column chromatography on silica gel (EtOAc:hexanes = 30:70) as a colourless solid (39 mg, 66%, 0.1 mmol scale); R_f (EtOAc/hexanes = 30:70) 0.55; mp: 102-104 °C; IR (DCM): 3379, 2953, 1742, 1513 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ_H 8.60-8.55 (2H, m), 8.14 (1H, d, J = 7.8 Hz), 7.85 (1H, td, J_1 = 7.7 Hz, J_2 = 1.7 Hz), 7.47-7.44 (1H, m), 7.30-7.26 (4H, m), 7.20 (2H, t, J = 7.2 Hz), 7.13 (4H, d, J = 7.4 Hz), 6.47 (2H, s), 5.04 (1H, q, J = 8.1 Hz), 4.11 (4H, s), 3.71 (3H, s), 3.21-3.10 (2H, m), 0.90 (9H, s), 0.05 (6H, s); $^{13}C\{^1H\}$ NMR (~101 MHz, $CDCl_3$): δ_C 172.6, 163.9, 154.4, 149.3, 148.2, 141.4, 140.5, 137.3, 128.9, 128.4, 126.3, 126.2, 126.0, 122.3, 120.8, 52.8, 52.4, 39.1, 31.7, 25.7, 18.2, -4.5; HRMS (ESI): *m/z* $[M+H]^+$ calcd for $C_{36}H_{43}N_2O_4Si$: 595.2992; found: 595.2997. $[\alpha]^{25}_D$ = -7.3 (c = 0.03 g/mL, $CHCl_3$). The enantiomeric ratio (er 96:4) of compound **11a**-(L) was determined by using the Daicel Chiralcel OD column, hexane/*i*-PrOH 50:50, flow rate 1.0 mL/min, UV detection at 254 nm, t_D = 6.10 min, t_L = 8.26 min.

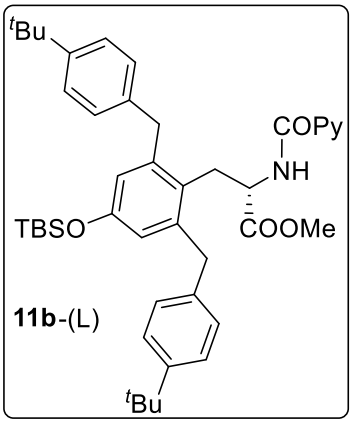


Methyl 3-(2,6-bis(4-(tert-butyl)benzyl)-4-((tert-butyldimethylsilyl)oxy)phenyl)-2-(picolinamido)propanoate (11b-(DL)): The compound **11b**-(DL) was obtained from procedure E after purification by column chromatography on silica gel (EtOAc:hexanes = 20:80) as a colourless solid (31 mg, 44%, 0.1 mmol scale); R_f (EtOAc/hexanes = 20:80) 0.7; mp: 117-119 ^{o}C; IR (DCM): 3386, 2957, 1742, 1512 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 8.60 (1H, d, J = 4.6 Hz), 8.56 (1H, d, J = 8.4 Hz), 8.14 (1H, d, J = 7.8 Hz), 7.85 (1H, td, J_1 = 7.7 Hz, J_2 = 1.6 Hz), 7.47-7.44 (1H, m), 7.30 (4H, d, J = 8.2 Hz), 7.06 (4H, d, J = 8.2 Hz), 6.42 (2H, s), 5.04 (1H, q, J = 8.1 Hz), 4.07 (4H, s), 3.72 (3H, s), 3.24-3.13 (2H, m), 1.32 (18H, s), 0.88 (9H, s), 0.02 (6H, s); ^{13}C{^{1}H} NMR (~101 MHz, $CDCl_3$): δ_C 172.7, 163.9, 154.3, 149.3, 148.8, 148.2, 141.5, 137.4, 137.3, 128.6, 126.3, 126.0, 125.3, 122.3, 120.6, 52.9, 52.3, 38.6, 34.4, 31.6, 31.4, 25.7, 18.3, -4.5; HRMS (ESI): *m/z* [M+Na]$^{+}$ calcd for $C_{44}H_{58}N_2O_4NaSi$: 729.4064; found: 729.4070.

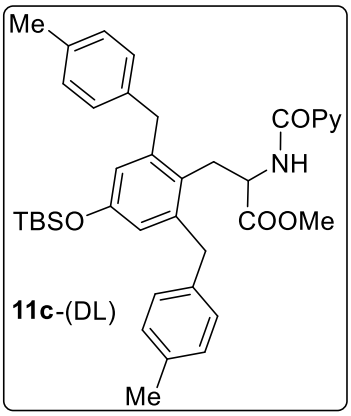


Methyl (*R*)-3-(2,6-bis(4-(tert-butyl)benzyl)-4-((tert-butyldimethylsilyl)oxy)phenyl)-2-(picolinamido)propanoate (11b-(D)): The compound **11b**-(D) was obtained from procedure E after purification by column chromatography on silica gel (EtOAc:hexanes = 20:80) as a colourless solid (42 mg, 59%, 0.1 mmol scale); R_f (EtOAc/hexanes = 20:80) 0.7; mp: 116-118 ^{o}C; IR (DCM): 3386, 2956, 1742, 1512 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 8.61 (1H, d, J = 4.3 Hz), 8.57 (1H, d, J = 8.4 Hz), 8.15 (1H, d, J = 7.8 Hz), 7.85 (1H, td, J_1 = 7.7 Hz, J_2 = 1.6 Hz), 7.48-7.44 (1H, m), 7.31 (4H, d, J = 8.2 Hz), 7.07 (4H, d, J = 8.2 Hz), 6.43 (2H, s), 5.05 (1H, q, J = 8.0 Hz), 4.07 (4H, s), 3.72 (3H, s), 3.24-3.14 (2H, m), 1.33 (18H, s), 0.88 (9H, s), 0.03 (6H, s); ^{13}C{^{1}H} NMR (~101 MHz, $CDCl_3$): δ_C 172.7, 163.9, 154.3, 149.3, 148.8, 148.2, 141.5, 137.4, 137.3, 128.6, 126.3, 126.1, 125.3, 122.3, 120.6, 52.9, 52.3, 38.6, 34.4, 31.6, 31.4, 25.7, 18.3, -4.5; HRMS (ESI): *m/z* [M+Na]$^{+}$ calcd for $C_{44}H_{58}N_2O_4NaSi$: 729.4064; found: 729.4063. $[\alpha]^{25}_{D}$ = +8.6 (c = 0.03 g/mL, $CHCl_3$).



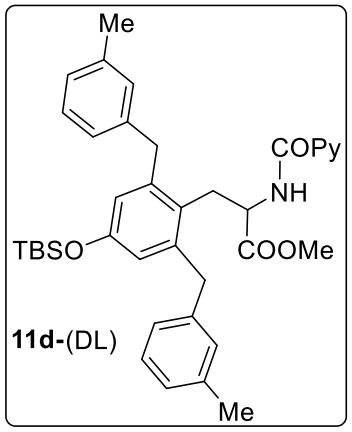
Methyl (*S*)-3-(2,6-bis(4-(tert-butyl)benzyl)-4-((tert-butyldimethylsilyl)oxy)phenyl)-2-(picolinamido)propanoate (11b-(L)): 

The compound **11b**-(L) was obtained from procedure E after purification by column chromatography on silica gel (EtOAc:hexanes = 20:80) as a colourless solid (48 mg, 65%, 0.1 mmol scale); R_f (EtOAc/hexanes = 20:80) 0.7; mp: 116-118 ^{o}C; IR (DCM): 3385, 2957, 1742, 1512 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 8.60 (1H, d, J = 4.4 Hz), 8.56 (1H, d, J = 8.3 Hz), 8.14 (1H, d, J = 7.8 Hz), 7.85 (1H, td, J_1 = 7.7 Hz, J_2 = 1.6 Hz), 7.47-7.44 (1H, m), 7.29 (4H, d, J = 8.5 Hz), 7.07 (4H, d, J = 8.2 Hz), 6.41 (2H, s), 5.03 (1H, q, J = 8.1 Hz), 4.06 (4H, s), 3.71 (3H, s), 3.23-3.12 (2H, m), 1.32 (18H, s), 0.87 (9H, s), 0.02 (6H, s); ^{13}C{^{1}H} NMR (~101 MHz, $CDCl_3$): δ_C 172.7, 163.9, 154.3, 149.3, 148.8, 148.2, 141.6, 137.4, 137.3, 128.6, 126.3, 126.1, 125.3, 122.3, 120.6, 52.9, 52.3, 38.6, 34.4, 31.6, 31.4, 25.7, 18.3, -4.5; HRMS (ESI): *m/z* $[M+Na]^+$ calcd for $C_{44}H_{58}N_2O_4NaSi$: 729.4064; found: 729.4067. $[\alpha]^{25}_D$ = -10.0 (c = 0.03 g/mL, $CHCl_3$).

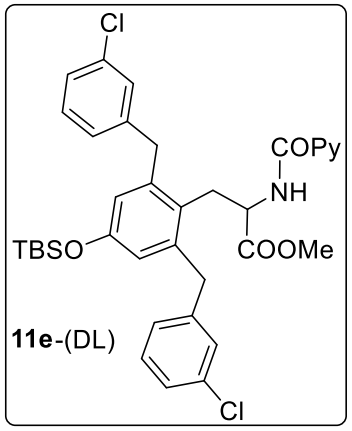
Methyl 3-(4-((tert-butyldimethylsilyl)oxy)-2,6-bis(4-methylbenzyl)phenyl)-2-(picolinamido)propanoate (11c-(DL)): 

The compound **11c**-(DL) was obtained from procedure E after purification by column chromatography on silica gel (EtOAc:hexanes = 30:70) as a colourless solid (38 mg, 61%, 0.1 mmol scale); R_f (EtOAc/hexanes = 30:70) 0.6; mp: 105-107 ^{o}C; IR (DCM): 3388, 2954, 1745, 1514 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 8.60-8.59 (1H, m), 8.55 (1H, d, J = 8.4 Hz), 8.13 (1H, d, J = 7.8 Hz), 7.85 (1H, td, J_1 = 7.7 Hz, J_2 = 1.6 Hz), 7.47-7.43 (1H, m), 7.08 (4H, d, J = 7.9 Hz), 7.00 (4H, d, J = 8.0 Hz), 6.48 (2H, s), 5.02 (1H, q, J = 8.1 Hz), 4.06 (4H, s), 3.71 (3H, s), 3.19-3.08 (2H, m), 2.33 (6H, s), 0.91 (9H, s), 0.07 (6H, s); ^{13}C{^{1}H} NMR (~101 MHz, $CDCl_3$): δ_C 172.7, 163.8, 154.3, 149.3, 148.2, 141.5, 137.4, 137.2, 135.4, 129.0, 128.7, 126.3, 126.2, 122.3, 120.8, 52.8, 52.3, 38.7, 31.6, 25.7, 21.0, 18.2, -4.5; HRMS (ESI): *m/z* $[M+H]^+$ calcd for $C_{38}H_{47}N_2O_4Si$: 623.3305; found: 623.3303.

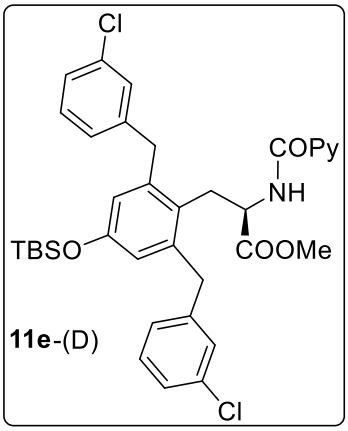
Methyl 3-(4-((tert-butyldimethylsilyl)oxy)-2,6-bis(3-methylbenzyl)phenyl)-2-(picolinamido)propanoate (11d-(DL)): The compound **11d**-(DL) was obtained from procedure E after purification by column chromatography on silica gel (EtOAc:hexanes = 30:70) as a colourless semi solid (31 mg, 50%, 0.1 mmol scale); R_f (EtOAc/hexanes = 30:70) 0.6; IR (DCM): 3386, 2930, 1743, 1513 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ_H 8.60-8.59 (1H, m), 8.55 (1H, d, J = 8.4 Hz), 8.14 (1H, d, J = 7.8 Hz), 7.85 (1H, td, J_1 = 7.7 Hz, J_2 = 1.7 Hz), 7.47-7.43 (1H, m), 7.16 (2H, t, J = 7.5 Hz), 7.01 (2H, d, J = 7.5 Hz), 6.94-6.91(4H, m), 6.48 (2H, s), 5.02 (1H, q, J = 8.0 Hz), 4.07 (4H, s), 3.72 (3H, s), 3.19-3.07 (2H, m), 2.29 (6H, s), 0.90 (9H, s), 0.07 (6H, s); $^{13}C\{^1H\}$ NMR (~101 MHz, $CDCl_3$): δ_C 172.7, 163.8, 154.3, 149.3, 148.2, 141.4, 140.4, 137.9, 137.3, 129.6, 128.2, 126.7, 126.3, 126.3, 125.9, 122.3, 120.9, 52.8, 52.3, 39.1, 31.7, 25.7, 21.4, 18.3, -4.4; HRMS (ESI): *m/z* $[M+Na]^+$ calcd for $C_{38}H_{46}N_2NaO_4Si$: 645.3125; found: 645.3136.



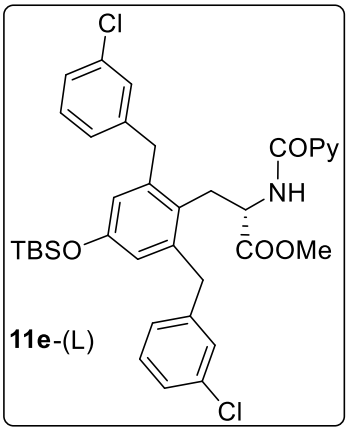
Methyl 3-(4-((tert-butyldimethylsilyl)oxy)-2,6-bis(3-chlorobenzyl)phenyl)-2-(picolinamido)propanoate (11e-(DL)): The compound **11e**-(DL) was obtained from procedure E after purification by column chromatography on silica gel (EtOAc:hexanes = 30:70) as a colourless solid (52 mg, 78%, 0.1 mmol scale); R_f (EtOAc/hexanes = 30:70) 0.6; mp: 76-78 ^oC; IR (DCM): 3375, 2952, 1741, 1512 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ_H 8.59 (1H, d, J = 4.6 Hz), 8.55 (1H, d, J = 8.5 Hz), 8.13 (1H, d, J = 7.8 Hz), 7.85 (1H, td, J_1 = 7.7 Hz, J_2 = 1.3 Hz), 7.47-7.44 (1H, m), 7.23-7.16 (4H, m), 7.08 (2H, s), 7.01 (2H, d, J = 7.1 Hz), 6.46 (2H, s), 5.00 (1H, q, J = 8.2 Hz), 4.09 (4H, s), 3.72 (3H, s), 3.08 (2H, d, J = 7.8 Hz), 0.90 (9H, s), 0.08 (6H, s); $^{13}C\{^1H\}$ NMR (~101 MHz, $CDCl_3$): δ_C 172.5, 163.8, 154.6, 149.1, 148.3, 142.5, 140.7, 137.3, 134.3, 129.6, 128.9, 127.0, 126.5, 126.3, 126.2, 122.3, 121.1, 52.7, 52.4, 38.8, 31.8, 25.7, 18.3, -4.4; HRMS (ESI): *m/z* $[M+H]^+$ calcd for $C_{36}H_{41}Cl_2N_2O_4Si$: 663.2213; found: 663.2222. The HPLC of compound **11e**-(DL) was determined by using the Daicel Chiralcel OD-H column, hexane/*i*-PrOH 80:20, flow rate 1.0 mL/min, UV detection at 254 nm, t_D = 8.27 min, t_L = 9.38 min.



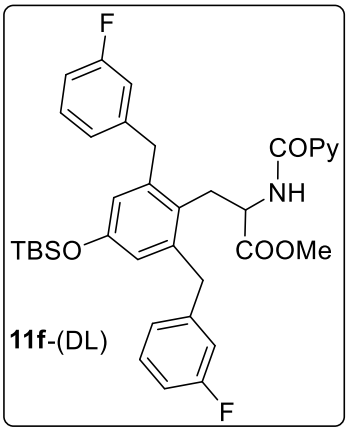
Methyl (*R*)-3-(4-((tert-butyldimethylsilyl)oxy)-2,6-bis(3-chlorobenzyl)phenyl)-2-(picolinamido)propanoate (11e-(D)): The compound **11e**-(D) was obtained from procedure E after purification by column chromatography on silica gel (EtOAc:hexanes = 30:70) as a colourless solid (55 mg, 83%, 0.1 mmol scale); R_f (EtOAc/hexanes = 30:70) 0.6; mp: 78-80 °C; IR (DCM): 3374, 2953, 1741, 1512 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ_H 8.60-8.59 (1H, m), 8.56 (1H, d, J = 8.6 Hz), 8.13 (1H, d, J = 7.8 Hz), 7.84 (1H, td, J_1 = 7.7 Hz, J_2 = 1.7 Hz), 7.47-7.43 (1H, m), 7.23-7.16 (4H, m), 7.09 (2H, s), 7.02 (2H, d, J = 7.1 Hz), 6.47 (2H, s), 5.00 (1H, q, J = 8.0 Hz), 4.10 (4H, s), 3.72 (3H, s), 3.09 (2H, d, J = 7.9 Hz), 0.91 (9H, s), 0.08 (6H, s); $^{13}C\{^1H\}$ NMR (~101 MHz, $CDCl_3$): δ_C 172.5, 163.8, 154.6, 149.1, 148.3, 142.5, 140.7, 137.3, 134.3, 129.6, 128.9, 127.0, 126.5, 126.3, 126.2, 122.3, 121.1, 52.7, 52.4, 38.8, 31.8, 25.7, 18.3, -4.4; HRMS (ESI): *m/z* $[M+H]^+$ calcd for $C_{36}H_{41}Cl_2N_2O_4Si$: 663.2213; found: 663.2223. $[\alpha]^{25}_D$ = +10.0 (c = 0.02 g/mL, $CHCl_3$). The enantiomeric ratio (er 98:2) of compound **11e**-(D) was determined by using the Daicel Chiralcel OD-H column, hexane/*i*-PrOH 80:20, flow rate 1.0 mL/min, UV detection at 254 nm, t_D = 8.26 min, t_L = 9.43 min.



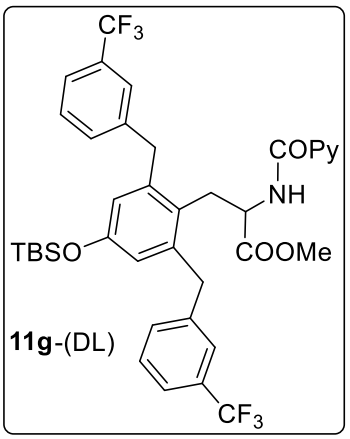
Methyl (*S*)-3-(4-((tert-butyldimethylsilyl)oxy)-2,6-bis(3-chlorobenzyl)phenyl)-2- (picolinamido)propanoate (11e-(L)): The compound **11e**-(L) was obtained from procedure E after purification by column chromatography on silica gel (EtOAc:hexanes = 30:70) as a colourless solid (54 mg, 81%, 0.1 mmol scale); R_f (EtOAc/hexanes = 30:70) 0.6; mp: 76-78 °C; IR (DCM): 3379, 2931, 1741, 1511 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ_H 8.59 (1H, d, J = 4.6 Hz), 8.56 (1H, d, J = 8.5 Hz), 8.12 (1H, d, J = 7.8 Hz), 7.85 (1H, td, J_1 = 7.7 Hz, J_2 = 1.6 Hz), 7.47-7.43 (1H, m), 7.23-7.16 (4H, m), 7.08 (2H, s), 7.01 (2H, d, J = 7.1 Hz), 6.46 (2H, s), 5.00 (1H, q, J = 8.0 Hz), 4.09 (4H, s), 3.72 (3H, s), 3.08 (2H, d, J = 7.9 Hz), 0.90 (9H, s), 0.08 (6H, s); $^{13}C\{^1H\}$ NMR (~101 MHz, $CDCl_3$): δ_C 172.5, 163.8, 154.6, 149.1, 148.3, 142.5, 140.7, 137.3, 134.3, 129.6, 128.9, 127.0, 126.4, 126.3, 126.2, 122.3, 121.1, 52.7, 52.4, 38.8, 31.8, 25.7, 18.3, -4.4; HRMS (ESI): *m/z* $[M+H]^+$ calcd for $C_{36}H_{41}Cl_2N_2O_4Si$: 663.2213; found: 663.2206. $[\alpha]^{25}_D$ = -10.9 (c = 0.02 g/mL, $CHCl_3$). The enantiomeric ratio (er 97:3) of compound **11e**-(L) was determined by using the Daicel Chiralcel OD-H column, hexane/*i*-PrOH 80:20, flow rate 1.0 mL/min, UV detection at 254 nm, t_D = 8.28 min, t_L = 9.37 min.

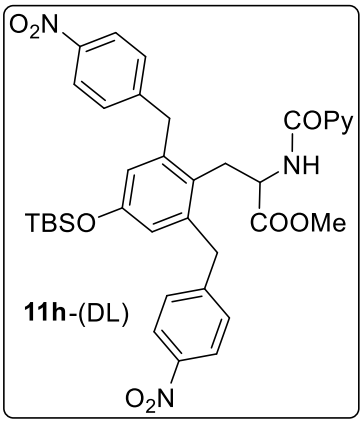


Methyl 3-(4-((tert-butyldimethylsilyl)oxy)-2,6-bis(3-fluorobenzyl)phenyl)-2-(picolinamido)propanoate (11f-(DL)): The compound **11f**-(DL) was obtained from procedure E after purification by column chromatography on silica gel (EtOAc:hexanes = 30:70) as a colourless solid (46 mg, 72%, 0.1 mmol scale); R_f (EtOAc/hexanes = 30:70) 0.55; mp: 80-82 ^{o}C; IR (DCM): 3387, 2954, 1742, 1513 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 8.60-8.59 (1H, m), 8.55 (1H, d, J = 8.5 Hz), 8.13 (1H, d, J = 7.8 Hz), 7.85 (1H, td, J_1 = 7.7 Hz, J_2 = 1.7 Hz), 7.47-7.44 (1H, m), 7.26-7.21 (2H, m), 6.93-6.79 (6H, m), 6.46 (2H, s), 5.00 (1H, q, J = 8.1 Hz), 4.10 (4H, s), 3.71 (3H, s), 3.10 (2H, d, J = 7.9 Hz), 0.90 (9H, s), 0.07 (6H, s); ^{13}C{^{1}H} NMR (~101 MHz, $CDCl_3$): δ_C 172.5, 163.9, 163.0 (d, J_{C-F} = 244.1 Hz), 154.5, 149.2, 148.2, 143.0 (d, J_{C-F} = 7.2 Hz), 140.8, 137.3, 129.7 (d, J_{C-F} = 32.8 Hz), 126.4, 126.2, 124.5 (d, J_{C-F} = 2.6 Hz), 122.3, 121.0, 115.7 (d, J_{C-F} = 21.3 Hz), 113.0 (d, J_{C-F} = 20.0 Hz), 52.7, 52.4, 38.8, 31.8, 25.7, 18.2, -4.5; ^{19}F{^{1}H} NMR (~376 MHz, $CDCl_3$): δ_F = -113.6; HRMS (ESI): *m/z* $[M+H]^+$ calcd for $C_{36}H_{41}F_2N_2O_4Si$: 631.2804; found: 631.2807.

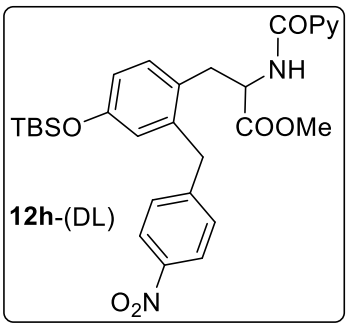


Methyl 3-(4-((tert-butyldimethylsilyl)oxy)-2,6-bis(3-(trifluoromethyl)benzyl)phenyl)-2-(picolinamido)propanoate (11g-(DL)): The compound **11g**-(DL) was obtained from procedure E after purification by column chromatography on silica gel (EtOAc:hexanes = 30:70) as a yellow coloured semi solid (76 mg, 69%, 0.15 mmol scale); R_f (EtOAc/hexanes = 30:70) 0.5; IR (DCM): 3382, 2932, 1742, 1512 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 8.62-8.58 (2H, m), 8.13 (1H, d, J = 7.8 Hz), 7.85 (1H, td, J_1 = 7.7 Hz, J_2 = 1.7 Hz), 7.47-7.43 (3H, m), 7.41-7.37 (4H, m), 7.32-7.30 (2H, m), 6.47 (2H, s), 5.04 (1H, q, J = 8.0 Hz), 4.19 (4H, s), 3.72 (3H, s), 3.08 (2H, d, J = 7.9 Hz), 0.89 (9H, s), 0.06 (6H, s); ^{13}C{^{1}H} NMR (~101 MHz, $CDCl_3$): δ_C 172.5, 163.8, 154.7, 149.1, 148.3, 141.4, 140.7, 137.3, 132.2, 130.7 (q, J_{C-F} = 31.9 Hz), 128.9, 126.5, 126.3, 125.4 (q, J_{C-F} = 3.2 Hz), 124.0 (q, J_{C-F} = 270.8 Hz), 123.0 (q, J_{C-F} = 3.5 Hz), 122.3, 121.3, 52.7, 52.4, 38.8, 32.0, 25.6, 18.3, -4.5; ^{19}F{^{1}H} NMR (~376 MHz, $CDCl_3$): δ_F = -62.6; HRMS (ESI): *m/z* $[M+H]^+$ calcd for $C_{38}H_{41}F_6N_2O_4Si$: 731.2740; found: 731.2737.

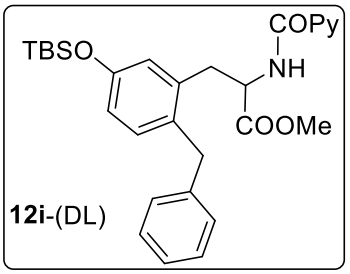


Methyl 3-(4-((tert-butyldimethylsilyl)oxy)-2,6-bis(4-nitrobenzyl)phenyl)-2-(picolinamido)propanoate (11h-(DL)): 

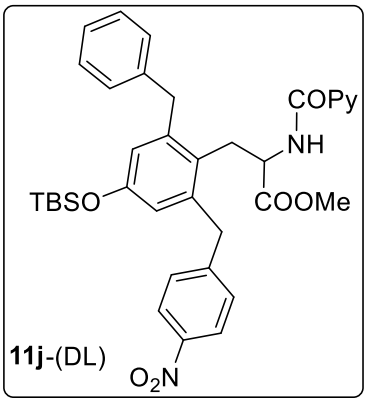
The compound **11h-**(DL) was obtained from procedure E after purification by column chromatography on silica gel (EtOAc:hexanes = 30:70) as a colourless semi solid (41 mg, 60%, 0.1 mmol scale); R_f (EtOAc/hexanes = 30:70) 0.3; IR (DCM): 3374, 2954, 1741, 1517 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ_H 8.56 (2H, d, J = 7.0 Hz), 8.11 (4H, d, J = 8.6 Hz), 8.13-8.09 (1H, m), 7.85 (1H, td, J_1 = 7.7 Hz, J_2 = 1.6 Hz), 7.47-7.44 (1H, m), 7.28 (4H, d, J = 8.6 Hz), 6.47 (2H, s), 5.00 (1H, dd, J_1 = 16.4 Hz, J_2 = 8.0 Hz), 4.21 (4H, s), 3.72 (3H, s), 3.06 (2H, d, J = 7.9 Hz), 0.89 (9H, s), 0.07 (6H, s); $^{13}C\{^1H\}$ NMR (~101 MHz, $CDCl_3$): δ_C 172.3, 163.9, 154.8, 149.0, 148.2, 148.2, 146.5, 140.2, 137.4, 129.5, 126.6, 126.3, 123.7, 122.3, 121.4, 52.8, 38.9, 32.5, 25.6, 18.2, -4.4; HRMS (ESI): *m/z* $[M+H]^+$ calcd for $C_{36}H_{41}N_4O_8Si$: 685.2694; found: 685.2681.

Methyl 3-(4-((tert-butyldimethylsilyl)oxy)-2-(4-nitrobenzyl)phenyl)-2-(picolinamido)propanoate (12h-(DL)): 

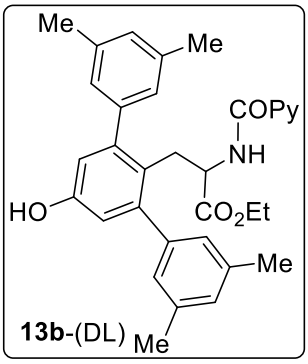
The compound **12h-**(DL) was obtained from procedure E after purification by column chromatography on silica gel (EtOAc:hexanes = 30:70) as a colourless semi solid (14 mg, 25%, 0.1 mmol scale); R_f (EtOAc/hexanes = 30:70) 0.3; IR (DCM): 3375, 2930, 1744, 1346 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ_H 8.55 (1H, d, J = 4.4 Hz), 8.45 (1H, d, J = 8.4 Hz), 8.12-8.08 (3H, m), 7.83 (1H, td, J_1 = 7.7 Hz, J_2 = 1.4 Hz), 7.45-7.42 (1H, m), 7.27 (2H, d, J = 8.0 Hz), 7.04 (1H, d, J = 8.3 Hz), 6.68 (1H, dd, J_1 = 8.3 Hz, J_2 = 2.5 Hz), 6.53 (1H, d, J = 2.4 Hz), 4.94 (1H, q, J = 7.1 Hz), 4.17 (1H, d, J = 16.6 Hz), 4.12 (1H, d, J = 16.4 Hz), 3.69 (3H, s), 3.15-3.03 (2H, m), 0.92 (9H, s), 0.11 (6H, s); $^{13}C\{^1H\}$ NMR (~101 MHz, $CDCl_3$): δ_C 172.1, 163.9, 155.0, 149.1, 148.4, 148.2, 146.5, 138.8, 137.4, 131.7, 129.5, 127.4, 126.5, 123.7, 122.4, 122.3, 118.9, 53.2, 52.4, 38.5, 35.3, 25.6, 18.2, -4.4; HRMS (ESI): *m/z* $[M+H]^+$ calcd for $C_{29}H_{36}N_3O_6Si$: 550.2373; found: 550.2361.

Methyl 3-(2-benzyl-5-((tert-butyldimethylsilyl)oxy)phenyl)-2-(picolinamido)propanoate (12i-(DL)): 

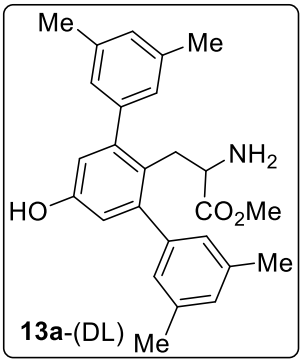
The compound **12i**-(DL) was obtained from procedure E after purification by column chromatography on silica gel (EtOAc:hexanes = 30:70) as a colourless semi solid (33 mg, 65%, 0.1 mmol scale); R_f (EtOAc/hexanes = 30:70) 0.6; IR (DCM): 3377, 2930, 1743, 1434 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ_H 8.59-8.57 (1H, m), 8.48 (1H, d, J = 8.4 Hz), 8.15 (1H, d, J = 7.8 Hz), 7.85 (1H, td, J_1 = 7.7 Hz, J_2 = 1.7 Hz), 7.46-7.43 (1H, m), 7.29-7.25 (2H, m), 7.21-7.17 (1H, m), 7.12 (2H, d, J = 7.0 Hz), 6.97 (1H, d, J = 8.1 Hz), 6.70-6.66 (2H, m), 5.02-4.96 (1H, m), 4.07 (1H, d, J = 19.4 Hz), 4.02 (1H, d, J = 19.4 Hz), 3.74 (3H, s), 3.24 (1H, dd, J_1 = 14.2 Hz, J_2 = 6.0 Hz), 3.04 (1H, dd, J_1 = 14.2 Hz, J_2 = 8.0 Hz), 0.94 (9H, s), 0.12 (3H, s), 0.11 (3H, s); $^{13}C\{^1H\}$ NMR (~101 MHz, $CDCl_3$): δ_C 172.1, 164.0, 154.0, 149.2, 148.2, 140.8, 137.3, 135.7, 132.0, 131.7, 128.7, 128.4, 126.4, 126.0, 122.3, 121.8, 118.9, 52.9, 52.4, 37.9, 35.5, 25.6, 18.1, -4.5; HRMS (ESI): *m/z* $[M+H]^+$ calcd for $C_{29}H_{37}N_2O_4Si$: 505.2523; found: 505.2530.

Methyl 3-(2-benzyl-4-((tert-butyldimethylsilyl)oxy)-6-(4-nitrobenzyl)phenyl)-2-(picolinamido)propanoate (11j-(DL)): 

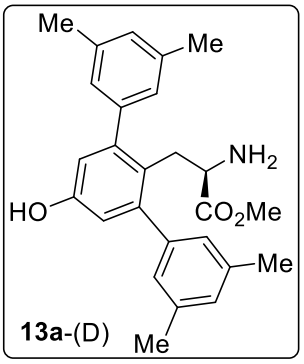
The compound **11j**-(DL) was obtained from procedure E after purification by column chromatography on silica gel (EtOAc:hexanes = 30:70) as a colourless semi solid (13 mg, 56%, 0.04 mmol scale); R_f (EtOAc/hexanes = 30:70) 0.3; IR (DCM): 3373, 2928, 1741, 1515 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ_H 8.58-8.54 (2H, m), 8.13-8.10 (3H, m), 7.86 (1H, td, J_1 = 7.7 Hz, J_2 = 1.7 Hz), 7.48-7.44 (1H, m), 7.30-7.26 (4H, m), 7.21 (1H, d, J = 7.3 Hz), 7.10 (2H, d, J = 7.0 Hz), 6.50 (1H, d, J = 2.6 Hz), 6.43 (1H, d, J = 2.6 Hz), 5.00 (1H, q, J = 8.0 Hz), 4.26 (1H, d, J = 16.7 Hz), 4.20 (1H, d, J = 16.7 Hz), 4.07 (2H, s), 3.71 (3H, s), 3.09 (2H, d, J = 8.1 Hz), 0.89 (9H, s), 0.06 (6H, s); $^{13}C\{^1H\}$ NMR (~101 MHz, $CDCl_3$): δ_C 172.4, 163.9, 154.6, 149.1, 148.6, 148.2, 146.4, 141.9, 140.2, 139.7, 137.3, 129.5, 128.8, 128.5, 126.5, 126.2, 126.2, 123.6, 122.3, 121.4, 120.8, 52.8, 52.4, 39.2, 38.9, 32.0, 25.7, 18.2, -4.4; HRMS (ESI): *m/z* $[M+H]^+$ calcd for $C_{36}H_{42}N_3O_6Si$: 640.2843; found: 640.2853.

Ethyl 3-(5'-hydroxy-3,3'',5,5''-tetramethyl-[1,1':3',1''-terphenyl]-2'-yl)-2-(picolinamido)propanoate (13b-(DL)): 

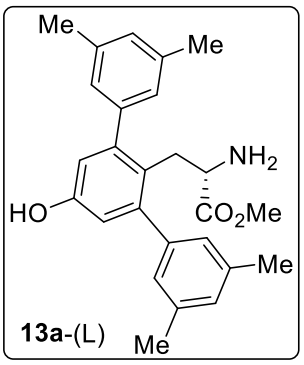
The compound **13b**-(DL) was obtained from procedure F after purification by column chromatography on silica gel (EtOAc:hexanes = 30:70) as a colourless solid (25 mg, 57%, 0.09 mmol scale); R_f (EtOAc/hexanes = 30:70) 0.4; mp: 221-223 ^{o}C; IR (DCM): 2985, 1733, 1251, 1048 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 8.54 (1H, d, J = 4.4 Hz), 8.04 (1H, d, J = 7.8 Hz), 7.92 (1H, d, J = 9.1 Hz), 7.75 (1H, td, J_1 = 7.7 Hz, J_2 = 0.7 Hz), 7.41-7.37 (1H, m), 6.97 (6H, s), 6.62 (2H, s), 4.51-4.45 (1H, m), 3.89 (2H, q, J = 7.1 Hz), 3.41 (1H, dd, J_1 = 14.2 Hz, J_2 = 3.4 Hz), 3.01 (1H, dd, J_1 = 14.1 Hz, J_2 = 11.1 Hz), 2.30 (12H, s), 1.05 (3H, t, J = 7.1 Hz); (The signal corresponding to OH was not precisely located in the proton NMR); ^{13}C{^{1}H} NMR (~101 MHz, $CDCl_3$): δ_C 171.8, 164.2, 154.1, 149.3, 148.1, 145.0, 141.7, 137.6, 137.2, 128.6, 127.3, 126.1, 123.3, 122.4, 116.5, 60.9, 53.0, 31.8, 21.4, 13.8; HRMS (ESI): *m/z* [M+H]$^{+}$ calcd for $C_{33}H_{35}N_2O_4$: 523.2597; found: 523.2604.

Methyl 2-amino-3-(5'-hydroxy-3,3'',5,5''-tetramethyl-[1,1':3',1''-terphenyl]-2'-yl)propanoate (13a-(DL)): 

The compound **13a**-(DL) was obtained from procedure G after purification by column chromatography on silica gel (EtOAc:hexanes = 50:50) as a yellow coloured solid (30 mg, 50%, 0.15 mmol scale); R_f (EtOAc/hexanes = 50:50) 0.2; mp: 103-105 ^{o}C; IR (DCM): 3357, 2948, 1738, 1445 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 6.99 (4H, s), 6.96 (2H, s), 6.60 (2H, s), 3.44 (3H, s), 3.28 (1H, dd, J_1 = 14.1 Hz, J_2 = 4.4 Hz), 3.06 (1H, dd, J_1 = 10.3 Hz, J_2 = 4.5 Hz), 2.72 (1H, dd, J_1 = 14.0 Hz, J_2 = 10.4 Hz), 2.32 (12H, s) (The signals corresponding to OH and NH_2 were not precisely located in the proton NMR); ^{13}C{^{1}H} NMR (~101 MHz, $CDCl_3$): δ_C 175.3, 154.0, 144.7, 141.9, 137.8, 128.7, 127.1, 123.4, 116.9, 53.7, 51.9, 33.9, 21.4; HRMS (ESI): *m/z* [M+H]$^{+}$ calcd for $C_{26}H_{30}NO_3$: 404.2226; found: 404.2235.

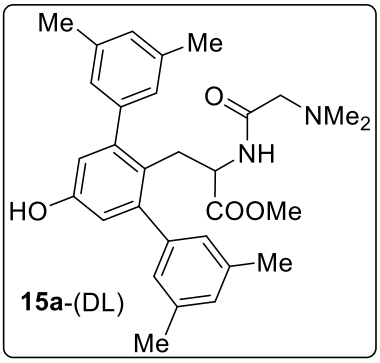
Methyl (*R*)-2-amino-3-(5'-hydroxy-3,3'',5,5''-tetramethyl-[1,1':3',1''-terphenyl]-2'-yl)propanoate (13a-(D)): 

The compound **13a**-(D) was obtained from procedure G after purification by column chromatography on silica gel (EtOAc:hexanes = 50:50) as a yellow coloured solid (210 mg, 52%, 1 mmol scale); R_f (EtOAc/hexanes = 50:50) 0.2; mp: 102-104 ^oC; IR (DCM): 3357, 2918, 1738, 1445 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ_H 7.01 (4H, s), 6.99 (2H, s), 6.61 (2H, s), 3.47 (3H, s), 3.31 (1H, dd, J_1 = 14.2 Hz, J_2 = 4.4 Hz), 3.08 (1H, dd, J_1 = 10.3 Hz, J_2 = 4.4 Hz), 2.74 (1H, dd, J_1 = 14.1 Hz, J_2 = 10.4 Hz), 2.35 (12H, s); (The signals corresponding to OH and NH_2 were not precisely located in the proton NMR); $^{13}C\{^1H\}$ NMR (~101 MHz, $CDCl_3$): δ_C 175.4, 154.0, 144.7, 141.9, 137.8, 128.7, 127.1, 123.4, 116.9, 53.7, 51.9, 33.7, 21.3; HRMS (ESI): *m/z* $[M+H]^+$ calcd for $C_{26}H_{30}NO_3$: 404.2226; found: 404.2245. $[\alpha]^{25}_D$ = +10.7 (c = 0.01 g/mL, $CHCl_3$).

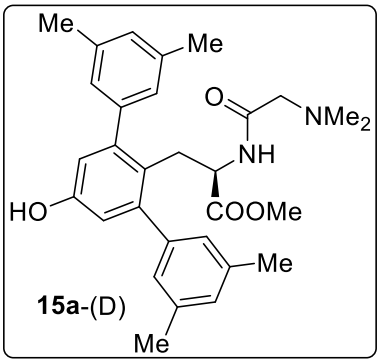
Methyl (*S*)-2-amino-3-(5'-hydroxy-3,3'',5,5''-tetramethyl-[1,1':3',1''-terphenyl]-2'-yl)propanoate (13a-(L)): 

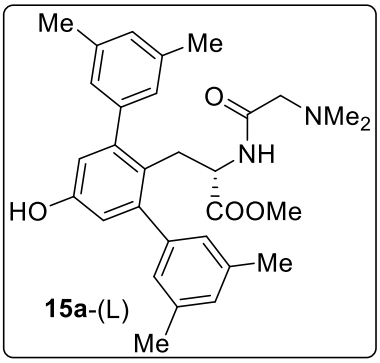
The compound **13a**-(L) was obtained from procedure G after purification by column chromatography on silica gel (EtOAc:hexanes = 50:50) as a yellow coloured solid (92 mg, 57%, 0.40 mmol scale); R_f (EtOAc/hexanes = 50:50) 0.2; mp: 102-104 ^oC; IR (DCM): 3355, 2920, 1738, 1445 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ_H 7.00 (4H, s), 6.99 (2H, s), 6.60 (2H, s), 3.47 (3H, s), 3.31 (1H, dd, J_1 = 14.2 Hz, J_2 = 4.4 Hz), 3.09 (1H, dd, J_1 = 10.4 Hz, J_2 = 4.4 Hz), 2.74 (1H, dd, J_1 = 14.2 Hz, J_2 = 10.4 Hz), 2.35 (12H, s); (The signals corresponding to OH and NH_2 were not precisely located in the proton NMR); $^{13}C\{^1H\}$ NMR (~101 MHz, $CDCl_3$): δ_C 175.4, 154.2, 144.6, 141.9, 137.7, 128.7, 127.1, 123.3, 117.0, 53.7, 51.9, 33.8, 21.4; HRMS (ESI): *m/z* $[M+H]^+$ calcd for $C_{26}H_{30}NO_3$: 404.2226; found: 404.2229. $[\alpha]^{25}_D$ = -12.2 (c = 0.01 g/mL, $CHCl_3$).

Methyl 2-(2-(dimethylamino)acetamido)-3-(5'-hydroxy-3,3'',5,5''-tetramethyl-[1,1':3',1''-terphenyl]-2'-yl)propanoate (15a-(DL)): The compound **15a**-(DL) was obtained from procedure C after purification by column chromatography on silica gel (EtOAc:hexanes = 50:50) as a colourless solid (41 mg, 84%, 0.1 mmol scale); R_f (EtOAc/hexanes = 50:50) 0.2; mp: 103-105 °C; IR (DCM): 3360, 2950, 1743, 1520 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ_H 6.99 (6H, s), 6.88 (1H, d, J = 8.7 Hz), 6.63 (2H, s), 4.22-4.14 (1H, m), 3.44 (3H, s), 3.37 (1H, dd, J_1 = 14.3 Hz, J_2 = 4.7 Hz), 2.88 (1H, dd, J_1 = 14.3 Hz, J_2 = 11.2 Hz), 2.81 (1H, d, J = 16.0 Hz), 2.76 (1H, d, J = 16.0 Hz), 2.35 (12H, s), 2.15 (6H, s); (The signal corresponding to OH was not precisely located in the proton NMR); $^{13}C\{^1H\}$ NMR (~101 MHz, $CDCl_3$): δ_C 172.4, 170.9, 154.4, 145.0, 141.6, 137.8, 128.8, 127.1, 122.6, 116.5, 62.7, 52.0, 51.3, 45.7, 31.1, 21.4; HRMS (ESI): *m/z* $[M+H]^+$ calcd for $C_{30}H_{37}N_2O_4$: 489.2753; found: 489.2764. The HPLC of compound **15a**-(DL) was determined by using the Daicel Chiralpak IC column, hexane/*i*-PrOH 80:20, flow rate 1.0 mL/min, UV detection at 254 nm, t_D = 9.03 min, t_L = 7.16 min.

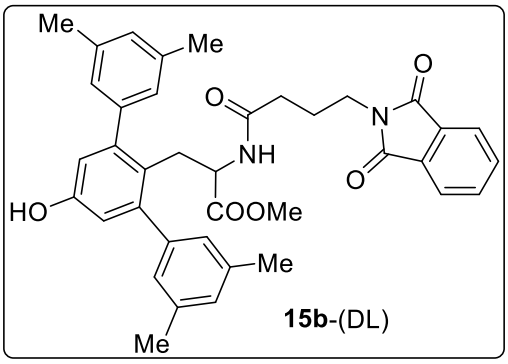


Methyl (*R*)-2-(2-(dimethylamino)acetamido)-3-(5'-hydroxy-3,3'',5,5''-tetramethyl-[1,1':3',1''-terphenyl]-2'-yl)propanoate (15a-(D)): The compound **15a**-(D) was obtained from procedure C after purification by column chromatography on silica gel (EtOAc:hexanes = 50:50) as a colourless solid (40 mg, 82%, 0.1 mmol scale); R_f (EtOAc/hexanes = 50:50) 0.2; mp: 104-106 °C; IR (DCM): 3337, 2948, 1744, 1521 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ_H 6.99 (6H, s), 6.86 (1H, d, J = 8.7 Hz), 6.65 (2H, s), 4.22-4.16 (1H, m), 3.44 (3H, s), 3.36 (1H, dd, J_1 = 14.3 Hz, J_2 = 4.7 Hz), 2.89 (1H, dd, J_1 = 14.2 Hz, J_2 = 11.2 Hz), 2.84 (1H, d, J = 15.7 Hz), 2.78 (1H, d, J = 15.7 Hz), 2.35 (12H, s), 2.17 (6H, s); (The signal corresponding to OH was not precisely located in the proton NMR); $^{13}C\{^1H\}$ NMR (~101 MHz, $CDCl_3$): δ_C 172.3, 170.6, 154.3, 145.0, 141.6, 137.8, 128.8, 127.1, 122.7, 116.4, 62.5, 52.0, 51.4, 45.6, 31.1, 21.3; HRMS (ESI): *m/z* $[M+H]^+$ calcd for $C_{30}H_{37}N_2O_4$: 489.2753; found: 489.2752. $[\alpha]^{25}_D$ = +10.0 (c = 0.02 g/mL, $CHCl_3$). The enantiomeric ratio (er 97:3) of compound **15a**-(D) was determined by using the Daicel Chiralpak IC column, hexane/*i*-PrOH 80:20, flow rate 1.0 mL/min, UV detection at 254 nm, t_D = 8.98 min, t_L = 7.05 min.



Methyl (*S*)-2-(2-(dimethylamino)acetamido)-3-(5'-hydroxy-3,3'',5,5''-tetramethyl-[1,1':3',1''-terphenyl]-2'-yl)propanoate (15a-(L)): 

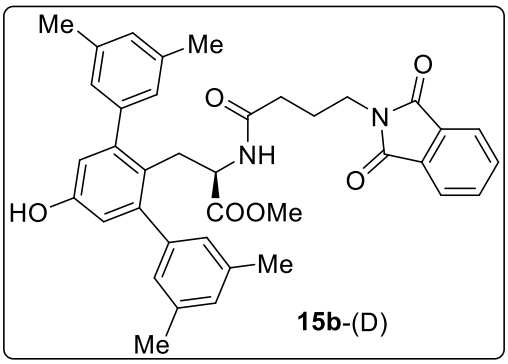
The compound **15a**-(L) was obtained from procedure C after purification by column chromatography on silica gel (EtOAc:hexanes = 50:50) as a colourless solid (26 mg, 72%, 0.074 mmol scale); R_f (EtOAc/hexanes = 50:50) 0.2; mp: 103-105 ^oC; IR (DCM): 3355, 2949, 1744, 1520 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ_H 6.97 (6H, s), 6.82 (1H, d, J = 8.8 Hz), 6.63 (2H, s), 4.20-4.14 (1H, m), 3.43 (3H, s), 3.34 (1H, dd, J_1 = 14.3 Hz, J_2 = 4.7 Hz), 2.86 (1H, dd, J_1 = 14.3 Hz, J_2 = 11.2 Hz), 2.80 (1H, d, J = 15.9 Hz), 2.74 (1H, d, J = 15.9 Hz), 2.33 (12H, s), 2.14 (6H, s); (The signal corresponding to OH was not precisely located in the proton NMR); $^{13}C\{^1H\}$ NMR (~101 MHz, $CDCl_3$): δ_C 172.3, 170.6, 154.2, 145.1, 141.5, 137.8, 128.8, 127.1, 122.9, 116.4, 62.7, 52.0, 51.3, 45.7, 31.1, 21.4; HRMS (ESI): *m/z* $[M+H]^+$ calcd for $C_{30}H_{37}N_2O_4$: 489.2753; found: 489.2744. $[\alpha]^{25}_D$ = -10.0 (c = 0.02 g/mL, $CHCl_3$). The enantiomeric ratio (er 97:3) of compound **15a**-(L) was determined by using the Daicel Chiralpak IC column, hexane/*i*-PrOH 80:20, flow rate 1.0 mL/min, UV detection at 254 nm, t_D = 9.14 min, t_L = 7.28 min.

Methyl 2-(4-(1,3-dioxoisoindolin-2-yl)butanamido)-3-(5'-hydroxy-3,3'',5,5''-tetramethyl-[1,1':3',1''-terphenyl]-2'-yl)propanoate (15b-(DL)): 

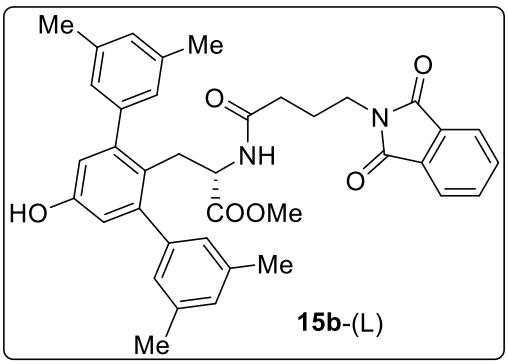
The compound **15b**-(DL) was obtained from procedure C after purification by column chromatography on silica gel (EtOAc:hexanes = 50:50) as a colourless solid (36 mg, 68%, 0.086 mmol scale); R_f (EtOAc/hexanes = 50:50) 0.3; mp: 98-100 ^oC; IR (DCM): 3358, 2923, 1708, 1441 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ_H 7.81 (2H, dd, J_1 = 5.4 Hz, J_2 = 3.0 Hz), 7.70 (2H, dd, J_1 = 5.4 Hz, J_2 = 3.1 Hz), 6.96 (2H, s), 6.94 (4H, s), 6.63 (2H, s), 5.37 (1H, d, J = 8.0 Hz), 4.15-4.10 (1H, m), 3.61 (2H, t, J = 6.7 Hz), 3.39 (3H, s), 3.21 (1H, dd, J_1 = 14.3 Hz, J_2 = 3.6 Hz), 2.94 (1H, dd, J_1 = 14.3 Hz, J_2 = 10.9 Hz), 2.32 (12H, s), 2.03-1.92 (2H, m), 1.88-1.79 (2H, m); (The signal corresponding to OH was not precisely located in the proton NMR); $^{13}C\{^1H\}$ NMR (~101 MHz, $CDCl_3$): δ_C 172.3, 171.6, 168.4, 154.1, 144.9, 141.6, 137.9, 134.0, 132.0, 128.8, 127.2, 123.5, 123.3, 116.6, 53.4, 52.0, 37.2, 33.4, 30.7, 24.6, 21.4; HRMS (ESI): *m/z* $[M+H]^+$

calcd for $C_{38}H_{39}N_2O_6$: 619.2808; found: 619.2795. The HPLC of compound **15b**-(DL) was determined by using the Daicel Chiralpak IC column, hexane/*i*-PrOH 70:30, flow rate 1.0 mL/min, UV detection at 254 nm, t_D = 14.43 min, t_L = 12.84 min.

Methyl (*R*)-2-(4-(1,3-dioxoisoindolin-2-yl)butanamido)-3-(5'-hydroxy-3,3'',5,5''-tetramethyl-[1,1':3',1''-terphenyl]-2'-yl)propanoate (15b-(D)): The compound **5b**-(D) was obtained from procedure C after purification by column chromatography on silica gel (EtOAc:hexanes = 50:50) as a colourless solid (26 mg, 42%, 0.1 mmol scale); R_f (EtOAc/hexanes = 50:50) 0.3; mp: 99-101 ^oC; IR (DCM): 3375, 2923, 1709, 1441 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ_H 7.84 (2H, dd, J_1 = 5.4 Hz, J_2 = 3.1 Hz), 7.72 (2H, dd, J_1 = 5.4 Hz, J_2 = 3.1 Hz), 6.99 (2H, s), 6.97 (4H, s), 6.67 (2H, s), 5.36 (1H, d, J = 8.0 Hz), 4.14 (1H, q, J = 7.2 Hz), 3.64 (2H, t, J = 6.7 Hz), 3.41 (3H, s), 3.23 (1H, dd, J_1 = 14.3 Hz, J_2 = 3.6 Hz), 2.96 (1H, dd, J_1 = 14.3 Hz, J_2 = 10.9 Hz), 2.35 (12H, s), 2.05-1.94 (2H, m), 1.90-1.82 (2H, m); (The signal corresponding to OH was not precisely located in the proton NMR); $^{13}C\{^1H\}$ NMR (~101 MHz, $CDCl_3$): δ_C 172.3, 171.5, 168.4, 154.0, 144.9, 141.5, 137.9, 134.0, 132.0, 128.8, 127.2, 123.6, 123.3, 116.5, 53.3, 52.0, 37.2, 33.4, 30.7, 24.6, 21.4; HRMS (ESI): *m/z* $[M+H]^+$ calcd for $C_{38}H_{39}N_2O_6$: 619.2808; found: 619.2806. $[\alpha]^{25}_D$ = +16.9 (c = 0.02 g/mL, $CHCl_3$). The enantiomeric ratio (er 96:4) of compound **15b**-(D) was determined by using the Daicel Chiralpak IC column, hexane/*i*-PrOH 70:30, flow rate 1.0 mL/min, UV detection at 254 nm, t_D = 14.51 min, t_L = 13.00 min.

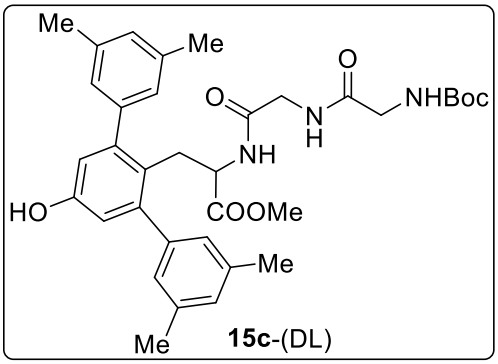


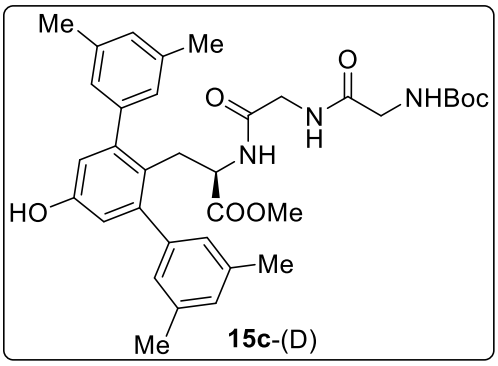
Methyl (*S*)-2-(4-(1,3-dioxoisoindolin-2-yl)butanamido)-3-(5'-hydroxy-3,3'',5,5''-tetramethyl-[1,1':3',1''-terphenyl]-2'-yl)propanoate (15b-(L)): The compound **15b**-(L) was obtained from procedure C after purification by column chromatography on silica gel (EtOAc:hexanes = 50:50) as a colourless solid (50 mg, 81%, 0.1 mmol scale); R_f (EtOAc/hexanes = 50:50) 0.3; mp: 98-100 ^oC; IR (DCM): 3406, 2946, 1708, 1441 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ_H 7.83 (2H, dd, J_1 = 5.4 Hz, J_2 = 3.0 Hz), 7.71 (2H, dd, J_1 = 5.4 Hz, J_2 = 3.1 Hz), 6.98 (2H, s), 6.97 (4H, s), 6.66 (2H, s), 5.42 (1H, d, J = 8.0



Hz), 4.17-4.11 (1H, m), 3.63 (2H, t, J = 6.7 Hz), 3.40 (3H, s), 3.22 (1H, dd, J_1 = 14.3 Hz, J_2 = 3.7 Hz), 2.96 (1H, dd, J_1 = 14.2 Hz, J_2 = 10.8 Hz), 2.35 (12H, s), 2.07-1.94 (2H, m), 1.89-1.82 (2H, m); (The signal corresponding to OH was not precisely located in the proton NMR); $^{13}C\{^1H\}$ NMR (~101 MHz, $CDCl_3$): δ_C 172.4, 171.7, 168.4, 154.3, 144.9, 141.6, 137.9, 134.0, 132.0, 128.8, 127.2, 123.3, 116.6, 53.4, 52.0, 37.2, 33.4, 30.7, 24.6, 21.3; HRMS (ESI): *m/z* $[M+H]^+$ calcd for $C_{38}H_{39}N_2O_6$: 619.2808; found: 619.2810. $[\alpha]^{25}_D$ = -19.9 (c = 0.02 g/mL, $CHCl_3$). The enantiomeric ratio (er 98:2) of compound **15b**-(L) was determined by using the Daicel Chiralpak IC column, hexane/*i*-PrOH 70:30, flow rate 1.0 mL/min, UV detection at 254 nm, t_D = 14.58 min, t_L = 12.91 min.

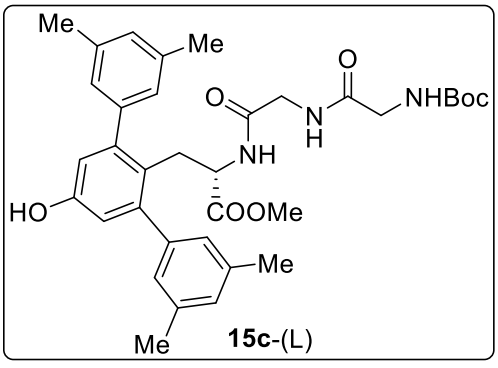
Methyl 12-((5'-hydroxy-3,3'',5,5''-tetramethyl-[1,1':3',1''-terphenyl]-2'-yl)methyl)-2,2-dimethyl-4,7,10-trioxo-3-oxa-5,8,11-triazatridecan-13-oate (15c-(DL)): The compound **15c**-(DL) was obtained from procedure C after purification by column chromatography on silica gel (EtOAc:hexanes = 50:50) as a colourless solid (38 mg, 83%, 0.074 mmol scale); R_f (EtOAc/hexanes = 50:50) 0.2; mp: 176-178 ^oC; IR (DCM): 3309, 2925, 1521, 1251 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ_H 6.98 (2H, s), 6.97 (4H, s), 6.78-6.77 (1H, m), 6.67 (2H, s), 5.50 (1H, d, J = 8.0 Hz), 5.34 (1H, s), 4.14-4.08 (1H, m), 3.78-3.73 (3H, m), 3.65-3.60 (1H, m), 3.40 (3H, s), 3.23 (1H, dd, J_1 = 14.4 Hz, J_2 = 3.9 Hz), 2.97 (1H, dd, J_1 = 14.0 Hz, J_2 = 11.0 Hz), 2.34 (12H, s), 1.40 (9H, s); (The signal corresponding to OH was not precisely located in the proton NMR); $^{13}C\{^1H\}$ NMR (~101 MHz, DMSO-d_6): δ_C 171.8, 169.8, 168.4, 156.2, 155.4, 144.9, 142.1, 137.5, 128.8, 127.2, 122.0, 116.5, 79.6, 78.5, 51.8, 43.6, 41.5, 28.6, 21.5; HRMS (ESI): *m/z* $[M+Na]^+$ calcd for $C_{35}H_{43}N_3NaO_7$: 640.2999; found: 640.2999. The HPLC of compound **15c**-(DL) was determined by using the Daicel Chiralpak IC column, hexane/*i*-PrOH 50:50, flow rate 1.0 mL/min, UV detection at 254 nm, t_D = 7.59 min, t_L = 13.06 min.





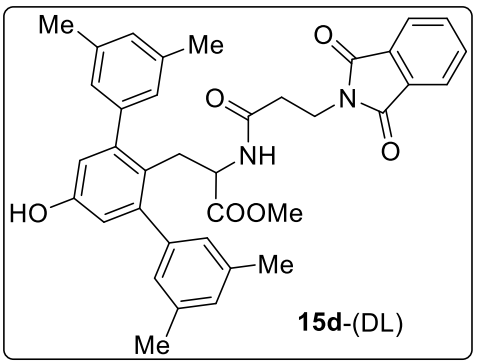
Methyl (*R*)-12-((5'-hydroxy-3,3'',5,5''-tetramethyl-[1,1':3',1''-terphenyl]-2'-yl)methyl)-2,2-dimethyl-4,7,10-trioxo-3-oxa-5,8,11-triazatridecan-13-oate (15c-(D)): The compound **15c**-(D) was obtained from procedure C after purification by column chromatography on silica gel (EtOAc:hexanes = 50:50) as a colourless solid (45 mg, 73%, 0.1 mmol scale); R_f (EtOAc/hexanes = 50:50) 0.2; mp: 177-179 ^oC; IR (DCM): 3331, 2925, 1523, 1251 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ_H 7.01 (2H, m), 6.99 (4H, m), 6.70 (2H, s), 5.44 (1H,d, J = 8.0 Hz), 5.30 (1H, s), 4.17-4.15 (1H, m), 3.81-3.78 (3H, m), 3.66-3.61 (1H, m), 3.44 (3H, s), 3.26 (1H, dd, J_1 = 14.4 Hz, J_2 = 3.6 Hz), 3.00 (1H, dd, J_1 = 13.7 Hz, J_2 = 11.2 Hz), 2.37 (12H, s), 1.44 (9H, s); (Two signals corresponding to OH and NH were not precisely located in the proton NMR); $^{13}C\{^1H\}$ NMR (~101 MHz, DMSO-d_6): δ_C 171.8, 169.8, 168.4, 156.2, 155.4, 144.9, 142.1, 137.5, 128.8, 127.2, 122.0, 116.5, 79.6, 78.5, 51.8, 43.6, 41.5, 28.6, 21.5; HRMS (ESI): *m/z* $[M+Na]^+$ calcd for $C_{35}H_{43}N_3O_7Na$: 640.2999; found: 640.3006. $[\alpha]^{25}_D$ = +17.9 (c = 0.04 g/mL, $CHCl_3$). The enantiomeric ratio (er 99:1) of compound **15c**-(D) was determined by using the Daicel Chiralpak IC column, hexane/*i*-PrOH 50:50, flow rate 1.0 mL/min, UV detection at 254 nm, t_D = 7.67 min, t_L = 13.01 min.

Methyl (*S*)-12-((5'-hydroxy-3,3'',5,5''-tetramethyl-[1,1':3',1''-terphenyl]-2'-yl)methyl)-2,2-dimethyl-4,7,10-trioxo-3-oxa-5,8,11-triazatridecan-13-oate (15c-(L)): The compound **15c**-(L) was obtained from procedure C after purification by column chromatography on silica gel (EtOAc:hexanes = 50:50) as a colourless solid (43 mg, 70%, 0.1 mmol scale); R_f (EtOAc/hexanes = 50:50) 0.2; mp: 175-177 ^oC; IR (DCM): 3331, 2925, 1522, 1251 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ_H 7.00 (2H, s), 6.98 (4H, s), 6.81-6.79 (1H, m), 6.69 (2H, s), 5.52 (1H,d, J = 8.0 Hz), 5.36 (1H, s), 4.17-4.11 (1H, m), 3.80-3.72 (3H, m), 3.67-3.62 (1H, m), 3.42 (3H, s), 3.26 (1H, dd, J_1 = 14.4 Hz, J_2 = 3.9 Hz), 2.99 (1H, dd, J_1 = 14.0 Hz, J_2 = 11.0 Hz), 2.36 (12H, s), 1.43 (9H, s); (The signal corresponding to OH was not precisely located in the proton NMR);$^{13}C\{^1H\}$ NMR (~101 MHz, DMSO-d_6): δ_C 171.8, 169.8, 168.4, 156.2, 155.4, 144.9, 142.1, 137.5, 128.8, 127.2, 122.0, 116.5, 79.6, 78.5, 51.8, 43.6, 41.5, 28.6,



21.4; HRMS (ESI): *m/z* $[M+Na]^+$ calcd for $C_{35}H_{43}N_3O_7Na$: 640.2999; found: 640.3007. $[\alpha]^{25}_D$ = -16.9 (c = 0.04 g/mL, $CHCl_3$). The enantiomeric ratio (er 98:2) of compound **15c**-(L) was determined by using the Daicel Chiralpak IC column, hexane/*i*-PrOH 50:50, flow rate 1.0 mL/min, UV detection at 254 nm, t_D = 7.61 min, t_L = 12.93 min.

Methyl 2-(3-(1,3-dioxoisoindolin-2-yl)propanamido)-3-(5'-hydroxy-3,3'',5,5''-tetramethyl-[1,1':3',1''-terphenyl]-2'-yl)propanoate (15d-(DL)): The compound **15d**-(DL) was obtained from procedure C after purification by column chromatography on silica gel (EtOAc:hexanes = 50:50) as a colourless semi solid (35 mg, 58%, 0.1 mmol scale); R_f (EtOAc/hexanes = 50:50) 0.3; IR (DCM): 3399, 2923, 1712, 1250 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ_H 7.80 (2H, dd, J_1 = 5.4 Hz, J_2 = 3.1 Hz), 7.70 (2H, dd, J_1 = 5.4 Hz, J_2 = 3.0 Hz), 6.98 (2H, s), 6.95 (4H, s), 6.64 (2H, s), 5.66 (1H, s), 5.18 (1H, d, J = 7.8 Hz), 4.13-4.06 (1H, m), 3.83 (2H, t, J = 8.0 Hz), 3.67 (3H, s), 3.19 (1H, dd, J_1 = 14.3 Hz, J_2 = 3.6 Hz), 2.94 (1H, dd, J_1 = 14.4 Hz, J_2 = 11.0 Hz), 2.38-2.36 (2H, m), 2.34 (12H, s); $^{13}C\{^1H\}$ NMR (~101 MHz, $CDCl_3$): δ_C 172.1, 169.2, 168.0, 153.9, 145.0, 141.4, 138.0, 133.9, 132.0, 129.0, 127.2, 123.6, 123.3, 116.5, 53.4, 51.9, 34.2, 34.0, 30.5, 21.4; HRMS (ESI): *m/z* $[M+Na]^+$ calcd for $C_{37}H_{36}N_2NaO_6$: 627.2471; found: 627.2471.



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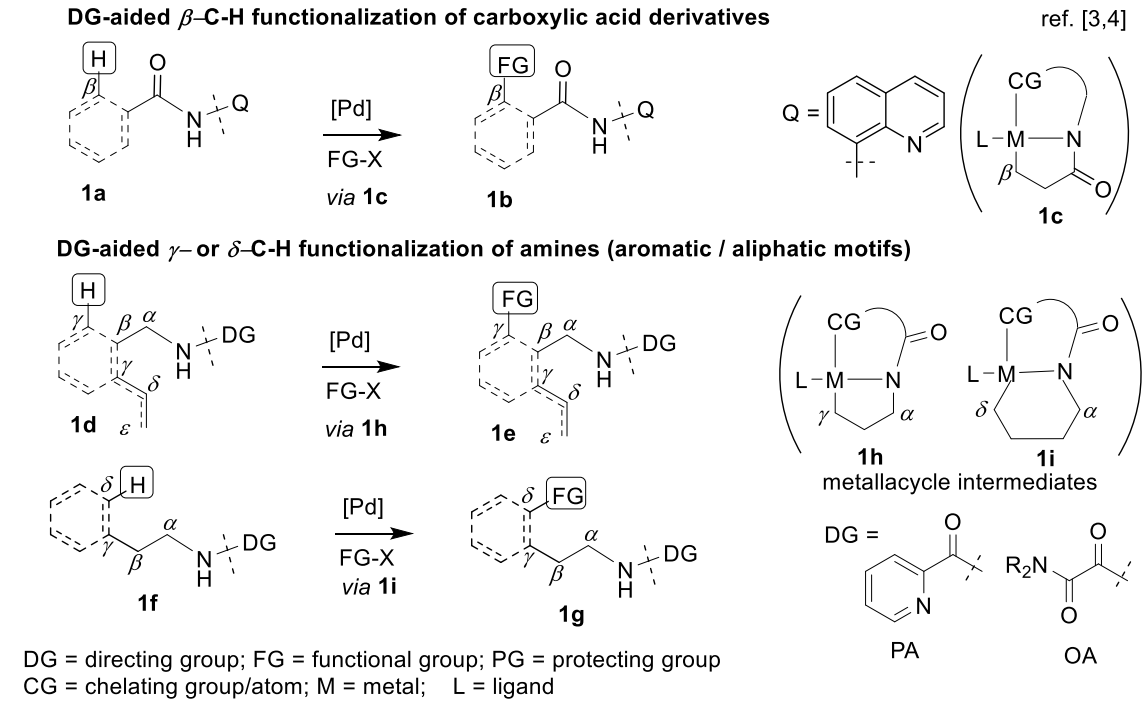
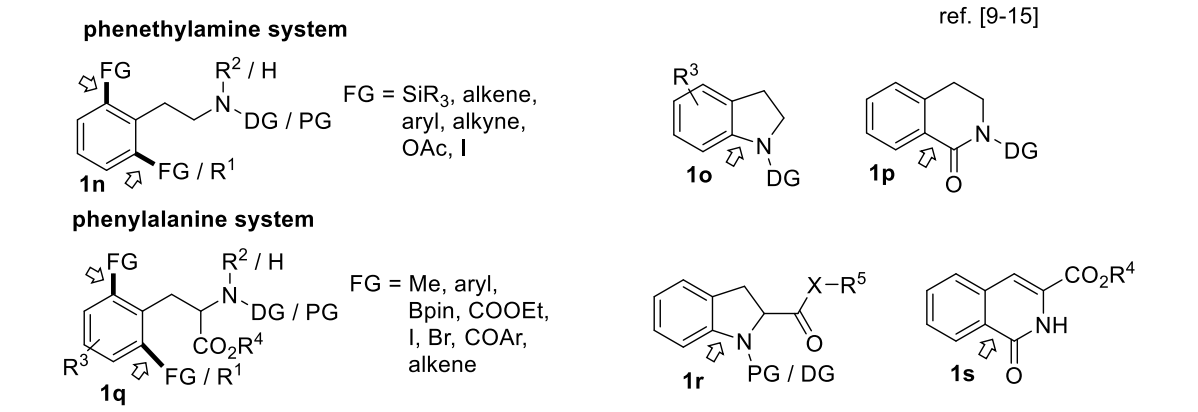
Chapter 4

Pd-Catalyzed Remote δ-C(sp^2)-H Functionalization in Phenylalaninol: Expanding the Library of Phenylalaninols

For the purpose of this thesis work, the work of chapter 4 is adapted with permission from the publication; Singh, P.; Babu, S. A.* *Synthesis* **2023**, *55,* A-AF. Title: Pd-Catalyzed Remote δ-C(sp^2)-H Functionalization in Phenylalaninol: Expanding the Library of Phenylalaninols

The transition metal-catalyzed C-H functionalization methods have emerged as important tools for installing functional groups in small organic molecules and the synthesis of functionalized organic compounds.[1-4] Substantial developments have occurred in the research area of Pd(II)-catalyzed, directing group (DG)-mediated, site-selective functionalization of sp^2 and sp^3 C-H bonds of carboxylic acid and amine substrates.[3-8] With regard to site-selectivity, the functionalization of the β-C-H bonds of carboxylic acid substrates **1a** has been extensively explored using the 8-aminoquinoline (AQ) type DGs (Scheme 1a).[3-5,7,8] In carboxylic acids, C-H bonds beyond the β-position are considered remote (e.g., γ- and δ-C-H bonds). On the other hand, the functionalization of γ-C-H bonds of amine substrates **1d** has been extensively explored using the picolinamide (PA) type DGs and these reactions are believed to undergo via a 5-membered metallacycle intermediate(e.g. **1h**, Scheme 1a).[3,6] For example, the functionalization of the *ortho* γ-C(sp^2)-H bonds of aromatic amine substrates including benzylamine phenylglycine and phenylglycinol derivatives **1j** have been well documented.[6a-g] In amine substrates, C-H bonds beyond the γ-position are considered to be remote (e.g., δ-C-H and ε-C-H bonds).[3,4,9-20] Reasonable number of reports disclosed the functionalization of the remote δ-C(sp^2)-H bond of aromatic and aliphatic amines[9-20] (**1f**, Scheme 1a) and only rare reports dealt with remote ε-C-H functionalization of amines[20] using the PA type DGs. The expansion of the substrate scope and generality of the directing group-aided functionalization of the remote sp^2 and sp^3 C-H bonds of small organic molecules has been a persistent objective of various research groups.[3,4] The δ-C(sp^2)-H functionalization of phenylalanine or simple phenethylamine systems affording the corresponding products e.g. **1n,o,p** and **1q,r,s** have been established.[9-15] Especially, the Pd(II)-catalyzed DG-aided intermolecular δ-C(sp^2)-H functionalization of phenylalanine/tyrosine or simple phenethylamine derivatives through arylation, alkylation, halogenation, alkenylation, etc yielding the corresponding products **1n,q** are well explored (Scheme 1a).[3i,j,9-13]

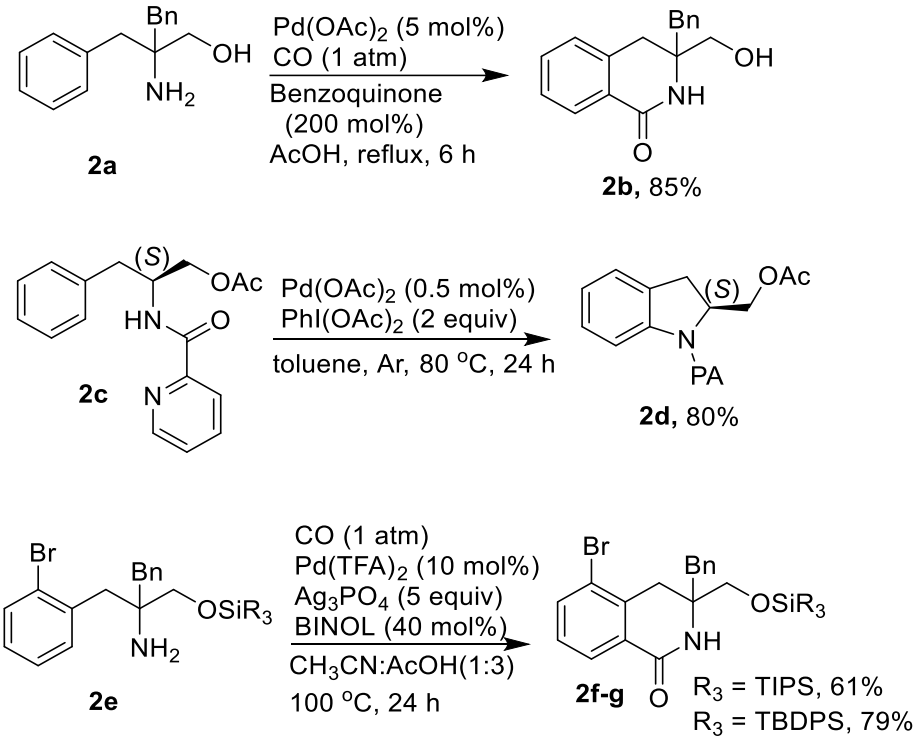




Scheme 1a: Directing group aided δ-C(sp^2)-H functionalization.

With regard to C-H functionalization of phenylalaninol, Granell's group in 2011[17a] disclosed a facile synthesis of benzolactams **2b** *via* Pd(II)-catalyzed carbonylation of unprotected phenylalaninol using amine as a directing group. The reaction pathway shows higher selectivity towards the formation of 6 membered ring over 5 membered ring due to the steric hindrance around amino group (Scheme 1b). Chen and co-workers in 2012[16] reported a Pd(II)-catalyzed intramolecular C(sp^2)–H (*ortho*) amination of phenylalaninol which led to the synthesis of indoline moiety. The optimum reaction condition uses substrate **2c** (1 equiv), $Pd(OAc)_2$ (0.5 mol%), $PhI(OAc)_2$ (2 equiv) in toluene at 80 ^oC for 24 h under argon atm to give C-H aminated product **2d** in 80% yield. Later in 2016, Kondo's group[17c] developed a highly chemoselective

method for the synthesis of benzolactams **2f-g** *via* Pd(II)-catalyzed intramolecular aminocarbonylation of Br-functionalized phenylalaninol. The remaining Br group in the cyclized product was further utilized for synthetic utilities such as Pd-catalyzed cross coupling reactions (Scheme 1b).



Scheme 1b: Representative examples of C-H functionalization of phenylalaninols

Phenylalaninol motif **1m** is a member of the phenethylamine family and is an important class of aromatic compounds in organic synthesis and medicinal chemistry.[21-23] Various phenylalaninols have been used as chiral ligands, auxiliaries and building blocks in the synthesis of natural products and synthetic bio-active/medicinally important molecules.[21-23] Phenylalaninol units are found in some natural products e.g., aurantiamide, aurantiamide acetate (Matijin-Su, which is used for treating chronic liver diseases) and cordyceamides A and B, (Figure 1).[22,23] A wide range of synthetically derived Matijin-Su scaffolds were prepared and found to exhibit potential biological activities (e.g., antihepatitis B virus, anticancer and anti-inflammatory, cytotoxic activities).[23] Furthermore, phenylalaninol-derived compounds were found to show potential bio-activities (e.g., HIV-1 protease inhibition and growth hormone-releasing activities).[22]

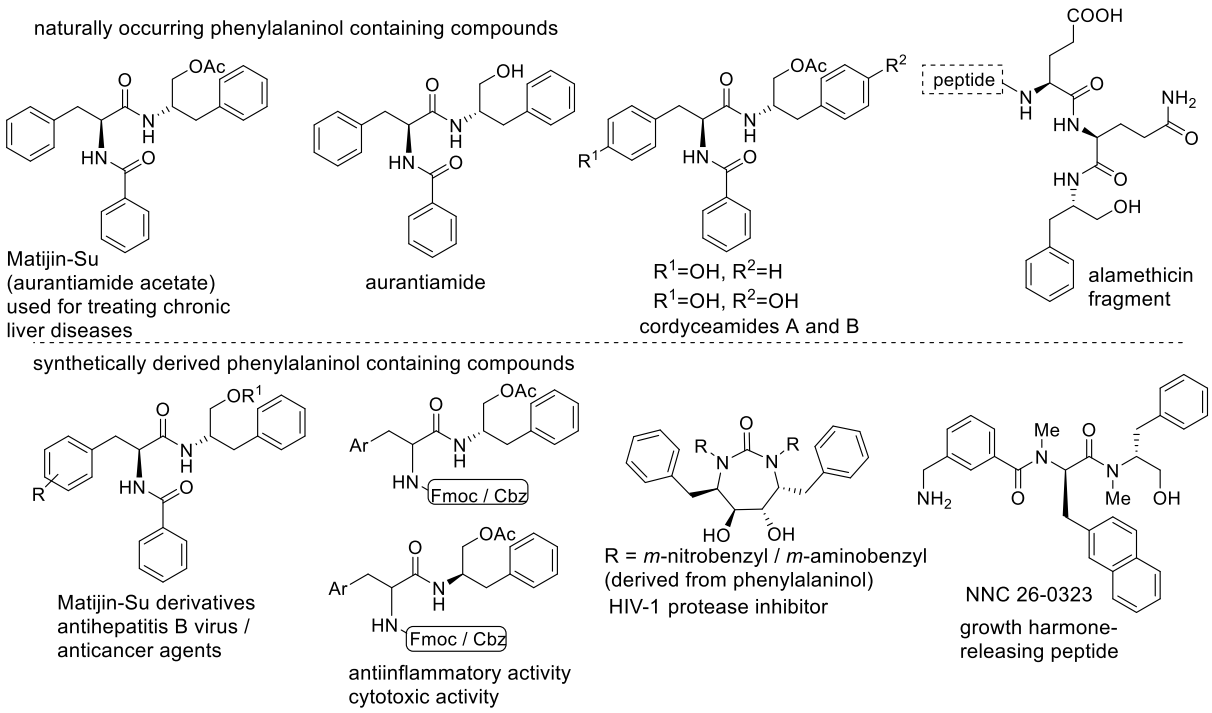


Figure 1: Examples of bioactive phenylalaninol-based compounds.

Phenylalaninol is a congener substrate to phenylalanine. While Jiang reported[6a] δ-C(sp^2)-H arylation of racemic phenylalanine and synthesis of racemic phenylalanine unnatural amino acid derivatives. Given the importance of chiral phenylalanine and phenylalaninol derivatives and the presence of enantiopure phenylalaninol units in bio-active substrates (Figure 1). Detailed herein are the Pd(II)-catalyzed, picolinamide-directed intermolecular δ-C(sp^2)-H (*ortho*) arylation, alkylation, halogenation, alkenylation of racemic and enantiopure phenylalaninol scaffolds (Figure 2). This approach has led to the assembling of a library of racemic and enantiopure *ortho* C-H arylated (phenylalaninol-based biaryl/terphenyl motifs), iodinated, brominated, alkylated phenylalaninol motifs.

Table 1 shows the screening of reaction conditions comprising the δ-C(sp^2)-H arylation of *O*-acetylated phenylalaninol substrate **3a**-(RS)) possessing the picolinamide DG with *p*-anisyl iodide (**4a**). The screening of reaction conditions was carried out using various Pd(II) catalysts, silver salt additives and solvents which are generally employed in the literature.[3,6,9-13] A silver salt (e.g., AgOAc, Ag_2CO_3) or an alkali metal-based salt (e.g., KOAc, CsOAc) is commonly employed as the halide ion scavenger (Daugulis's condition).[3,5a,9a] This process helps to regenerate the Pd(II) catalyst in the proposed bidentate DG-aided Pd^{II}-Pd^{IV} catalytic cycle.[3,5a]

Result and discussion:

Initially, we carried out the *δ*-C-H arylation of **3a**-(RS) with **4a** (5 equiv) in the presence of the $Pd(OAc)_2$ catalyst (10 mol%) and AgOAc additive (2.2 equiv) in toluene at 110 ^oC for 48 h. While this reaction is expected to afford the bis *δ*-C-H (*ortho*) arylated product **6a**-(RS) (phenylalaninol-based terphenyl derivative) and mono *δ*-C-H (*ortho*) arylated product **5a**-(RS) (phenylalaninol-based biaryl derivative). Notably, this reaction gave the bis *δ*-C-H (*ortho*) arylated phenylalaninol derivative **6a**-(RS) in 35% yield. The other expected mono *δ*-C-H (*ortho*) arylated derivative **5a**-(RS) was not obtained in a characterizable amount (entry 1, Table 1). Next, the same reaction was performed using KOAc as the additive instead of AgOAc and this reaction afforded the product **6a**-(RS) in 25% yield and **5a**-(RS) was not obtained (entry 2, Table 1).

Then, we performed the arylation of **3a**-(RS) with **4a** using NaOAc or CsOAc as the additive and these trials did not yield the expected products **5a**-(RS)/**6a**-(RS) (entries 3 and 4, Table 1). We then performed the C-H arylation of **3a**-(RS) with **4a** in the presence of the $Pd(OAc)_2$ catalyst and Ag_2CO_3 additive in *t*-amylOH (conditions reported by Daugulis, Chen, Jiang).[5a,i,6a,9a] This trial afforded the product **6a**-(RS) in 64% yield and **5a**-(RS) was not obtained (entry 5, Table 1). The same reaction in 1,4-dioxane gave the product **6a**-(RS) in 65% yield (entry 6, Table 1). The C-H arylation of **3a**-(RS) with **4a** using $Pd(TFA)_2$ as the catalyst did not yield any product. The C-H arylation of **3a**-(RS) using $PdCl_2$ as the catalyst afforded the product **6a**-(RS) in 24% yield and **5a**-(RS) was not obtained (entries 7 and 8, Table 1).

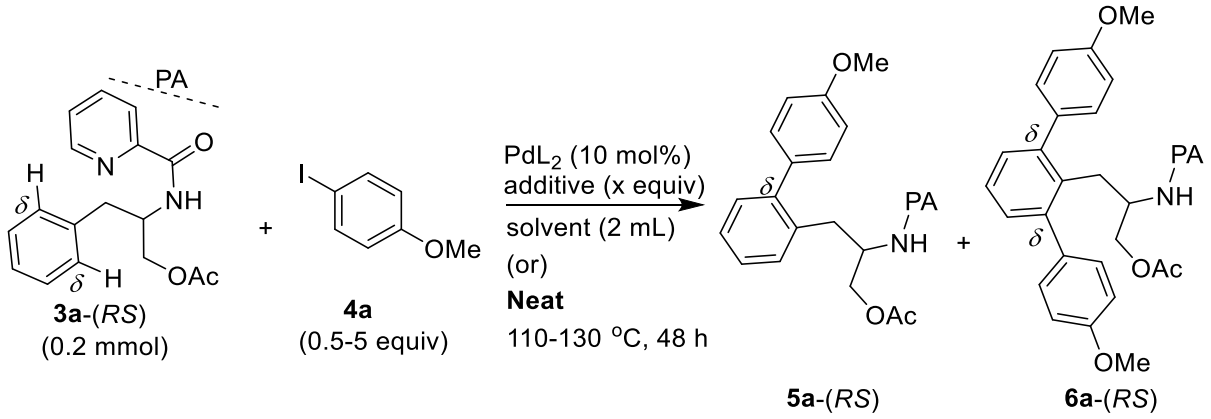
Next, to improve the yield, we intended to perform the *δ*-C-H (*ortho*) arylation of **3a**-(RS) under neat conditions without using any solvent. Accordingly, we heated **3a**-(RS) with **4a** (5 equiv) in the presence of the $Pd(OAc)_2$ catalyst (10 mol%) and Ag_2CO_3 additive (2.5 equiv) under neat conditions at 130 ^oC for 48 h. This reaction afforded the bis *δ*-C-H arylated derivative **6a**-(RS) in 70% yield. The mono *δ*-C-H arylated derivative **5a**-(RS) was not obtained in a characterizable amount (entry 9, Table 1).

Next, we wished to find out the suitable condition and amount of aryl iodide **4a** for obtaining the mono *δ*-C-H (*ortho*) arylated phenylalaninol derivative **5a**-(RS). Accordingly, we attempted the C-H arylation of **3a**-(RS) using 3 (or) 1 (or) 0.5 equiv of **4a**. The C-H arylation of **3a**-(RS) with 3 equiv of **4a** yielded **6a**-(RS) in 53% yield and did not yield **5a**-(RS) (entry 10, Table 1). The C-H arylation of **3a**-(RS) with 1 equiv of **4a** yielded **6a**-(RS) in 14% yield. Notably, this attempt was found to yield the mono (*ortho*) *δ*-C-H arylated derivative **5a**-(RS)

in a demonstrable yield of 11% (entry 11, Table 1). The C-H arylation of **3a**-(RS) with 0.5 equiv of **4a** did not yield **6a**-(RS) and **5a**-(RS) (entry 12, Table 1).

Taking an impetus from the conditions of entries 1 and 9, we then wished to change the amount of AgOAc or Ag_2CO_3 additive to find out whether the yield of **5a**-(RS) and **6a**-(RS) can be improved. The C-H arylation of **3a**-(RS) with **4a** using 2.5 or 5 equiv of AgOAc yielded **6a**-(RS) in 60 and 80% yields (entries 13 and 14, Table 1). While using excess amounts of AgOAc gave a high yield, however, the usage of 5 equiv of silver salt may not be an ideal condition under neat conditions. Finally, we performed the C-H arylation of **3a**-(RS) with **4a** using 0.5 or 1 or 1.5 equiv of Ag_2CO_3 and these trials gave **6a**-(RS) in 40, 52, and 60% yields (entries 13 and 14, Table 1). Based on these trials we preferred the condition of the reaction involving 2.5 equiv Ag_2CO_3 which afforded **6a**-(RS) in relatively good yield (70%). The other expected product **5a**-(RS) was not obtained in a characterizable amount in the attempts shown in entries 13-17 (Table 1).

Table 1: Screening of reaction condition for the *ortho*-*δ*-C-H-arylation of phenylalaninol substrates 3a-(*RS*):



entry	PdL_2 [10 mol%]	4a [equiv]	Additive [x equiv]	solvent	T [°C]	5a-(RS): yield [%]	6a-(RS): yield [%]
1[a]	$Pd(OAc)_2$	5	AgOAc (2.2)	toluene	110	-[d]	35
2[a]	$Pd(OAc)_2$	5	KOAc (2.0)	toluene	110	-	25
3[a]	$Pd(OAc)_2$	5	NaOAc (2.0)	toluene	110	-	-
4[a]	$Pd(OAc)_2$	5	CsOAc (2.0)	toluene	110	-	-

5[a]	$Pd(OAc)_2$	5	Ag_2CO_3 (2.5)	*t*-amylOH	130	-	64
6[a]	$Pd(OAc)_2$	5	Ag_2CO_3 (2.5)	1,4-dioxane	110	-	65
7[a]	$Pd(TFA)_2$	5	AgOAc (2.0)	toluene	110	-	-
8[a]	$PdCl_2$	5	AgOAc (2.0)	neat	110	-	24
9[b]	**$Pd(OAc)_2$**	**5**	**Ag_2CO_3 (2.5)**	**neat**	**130**	**-**	**70 [58]**[c]
10[b]	$Pd(OAc)_2$	3	Ag_2CO_3 (2.5)	neat	130	-	53
11[b]	$Pd(OAc)_2$	1	Ag_2CO_3 (2.5)	neat	130	11	14
12[b]	$Pd(OAc)_2$	0.5	Ag_2CO_3 (2.5)	neat	130	-	-
13[b, d]	$Pd(OAc)_2$	5	AgOAc (2.5)	neat	130	-	60
14[b, d]	$Pd(OAc)_2$	5	AgOAc (5)	neat	130	-	80
15[b, d]	$Pd(OAc)_2$	5	Ag_2CO_3 (0.5)	neat	130	-	40
16[b, d]	$Pd(OAc)_2$	5	Ag_2CO_3 (1.0)	neat	130	-	52
17[b, d]	$Pd(OAc)_2$	5	Ag_2CO_3 (1.5)	neat	130	-	60

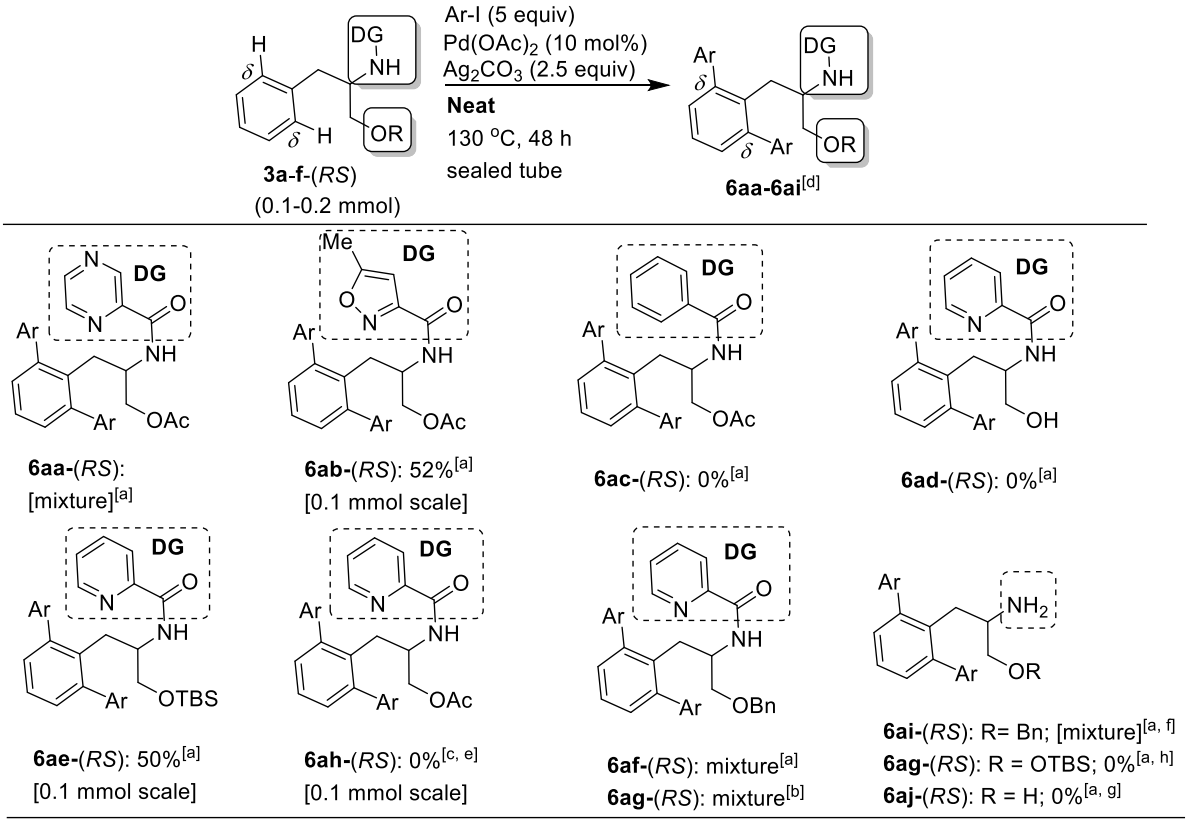
[a] Reactions were done in a RB flask. [b] Reactions were done in a sealed/pressure tube filled with ambient air. [c] Reaction period = 24 h. [[d] Reaction was done on a 0.1 mmol scale. [e] The – in all places refers that the expected product being undetectable in TLC (or) not obtained.

Having done the Pd(II)-catalyzed *δ*-C-H arylation reaction of phenylalaninol assisted by picolinamide DG, we wished to test the *δ*-C-H arylation of phenylalaninol by using other directing groups. The Pd(II)-catalyzed C-H arylation of phenylalaninol substrate **3b**-(RS) possessing the pyrazine-2-carboxamide DG (used by us earlier)[9k] yielded an inseparable mixture of the expected product **6aa**-(RS) with starting material **3b**-(RS) (Scheme 2). Next, we performed the Pd(II)-catalyzed C-H arylation of phenylalaninol substrate **3c**-(RS) possessing the 5-methylisoxazole-3-carboxamide DG (MICA DG, used by Liu).[6k] This reaction afforded the bis *δ*-C-H (*ortho*) arylated phenylalaninol derivative **6ab**-(RS) in 52% yield. The Pd(II)-catalyzed C-H arylation of phenylalaninol substrate **3d**-(RS) possessing the simple amide DG

did not yield the expected product **6ac**-(RS) The Pd(II)-catalyzed C-H arylation of phenylalaninol substrate **3e**-(RS) possessing the picolinamide DG and unprotected OH group did not yield the expected product **6ad**-(RS).

Based on literature works and our earlier experience of using *O*-acetylated phenylglycinol possessing the picolinamide DG as substrate;[6c-e,9b,13d,16] we attempted the C-H arylation reaction using the *O*-acetylated phenylalaninol substrate **3a**-(RS) possessing the picolinamide DG (Table 1). Along this line, we also assembled *O*-TBS phenylalaninol[17c] substrate **3f**-(RS) possessing the picolinamide DG and performed the C-H arylation of **3f**-(RS). This reaction afforded the bis δ-C-H (*ortho*) arylated phenylalaninol derivative **6ae**-(RS) in 50% yield (Scheme 2). We then attempted the C-H arylation of *O*-Bn phenylalaninol substrate **3g**-(RS) possessing the picolinamide DG and these attempts did not give the expected products **6af**-(RS)/**6ag**-(RS). The Pd(II)-catalyzed C-H arylation of corresponding phenylalaninol substrate **3h**-(RS) possessing the free NH_2 and OBn/OTBS groups did not yield the expected products **6ai**-(RS)/**6ak**-(RS) (Scheme 2). Additionally, the Pd(II)-catalyzed C-H arylation of phenylalaninol substrate **3j**-(RS) possessing the free NH_2 and OH groups did not yield the expected product **6aj**-(RS) (Scheme 2).

The products **6a**-(RS) (Table 1), **6ab**-(RS) and **6ae**-(RS) (Scheme 2) were obtained in the neat medium of *p*-anisyl iodide (**4a**) (which has a low mp, 50-53 ^{o}C). Notably, a trial reaction of C-H arylation of **3a**-(RS) in 1-iodo-4-nitrobenzene medium (which has a high mp, 171-173 ^{o}C) failed to afford the expected product **6ah**-(RS). Overall, the screening of reaction conditions, directing and protecting groups (Table 1 and Scheme 2), indicated that the OAc-protecting group and picolinamide DG possessing phenylalaninol derivative (e.g., **3a**-(RS)) is a suitable substrate for accomplishing the δ-C(sp^2)-H arylation reaction.



[a] ArI = I-C_6H_4-OMe-(*p*), mp: 50-53 °C, [b] ArI = PhI. [c] ArI = I-C_6H_4-NO_2–(*p*).

[e] Reaction was done using I-C_6H_4-NO_2-(*p*), mp 171-173 °C.

[f] Corresponding substrate 3h-(RS) [0.2 mmol], 4a [3 equiv], Pd[OAc]$_2$ [10 mol%], Ag_2CO_3 [1.5 equiv], o-nitrobenzoic acid [30 mol%], AcOH [2 mL], 130 °C, 24 h

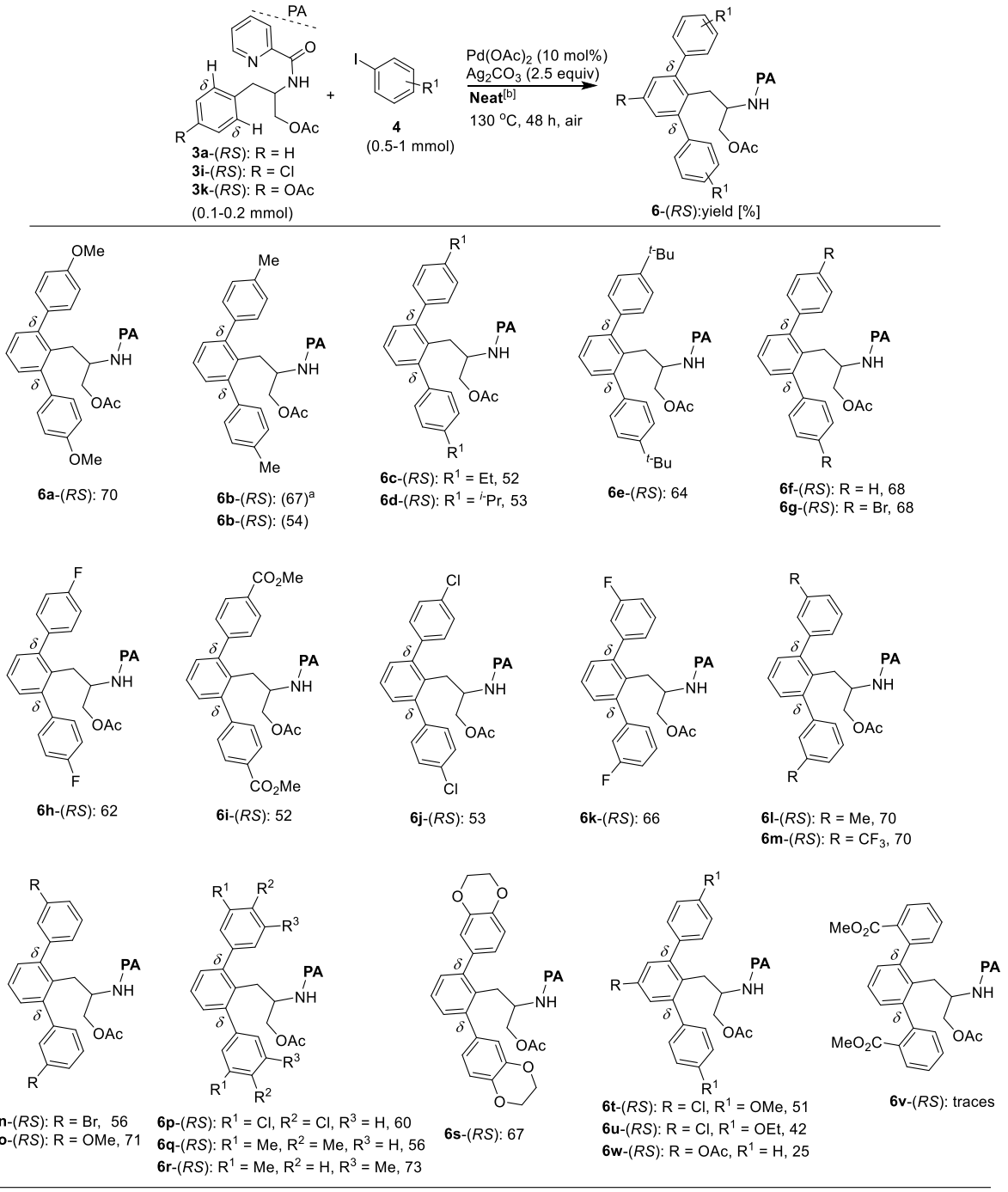
[g] Phenylalaninol [0.2 mmol], 4a [4 equiv], Pd[OAc]$_2$ [5 mol%], Ag_2O [0.75 equiv], HFIP/AcOH [85:15, 2 mL], 120 °C, 24 h.

[h] Corresponding substrate 3j-(*RS*) [0.2 mmol], 4a [4 equiv], Pd[OAc]$_2$ [5 mol%], Ag_2O [0.75 equiv], HFIP/AcOH [85:15, 2 mL], 120 °C, 24 h.

Scheme 2: Screening of directing and protecting groups for accomplishing the Pd(II)-catalyzed C-H arylation of phenylalaninols.

With the suitable reaction condition in hand, we then wished to demonstrate the substrate scope of this protocol comprising Pd(II)-catalyzed picolinamide-directed δ-C(sp^2)-H (*ortho*) arylation by using racemic and enantiopure phenylalaninol substrates. Scheme 3 reveals the $Pd(OAc)_2$-catalyzed, Ag_2CO_3-promoted, picolinamide-directed δ-C-H (*ortho*) arylation of the racemic substrate **3a**-(RS) with a variety of aryl iodides. The substrate **3a**-(RS) was treated with aryl iodides possessing a substituent at the para-position (e.g., OMe, Me, Et, *i*-Pr, *t*-Bu, Br, Cl, F and COOMe) and PhI in the presence of the $Pd(OAc)_2$ catalyst and Ag_2CO_3 additive

under neat conditions at 130 ºC for 48 h. These reactions gave the corresponding bis *δ*-C-H (*ortho*) arylated products **6a-j**-(RS) (phenylalaninol-based terphenyl derivatives) in 52-70% yields (Scheme 3). Then, the Pd(II)-catalyzed C-H arylation of **3a**-(RS) was performed using aryl iodides possessing a substituent at the meta-position (e.g., Br, F, Me, OMe and CF_3). These reactions gave the corresponding bis *δ*-C-H (*ortho*) arylated products **6k-o**-(RS) in 56-70% yields. Next, the Pd(II)-catalyzed C-H arylation of substrate **3a**-(RS) with disubstituted aryl iodides gave the corresponding bis *δ*-C-H (*ortho*) arylated products **6r,s**-(RS) in 67-73% yields (Scheme 3). Then the substrate **3i**-(RS) possessing a substituent at the para-position (e.g., Cl) was treated with para-substituted aryl iodides to afford the corresponding bis *δ*-C-H (*ortho*) arylated products **6t,u**-(RS) in 42-51% yields. Additionally, the Pd(II)-catalyzed C-H arylation of tyrosinol substrate **3k**-(RS) with PhI gave the bis *δ*-C-H (*ortho*) arylated product **6w**-(RS) in 25% yield (Scheme 3). It is a limitation that the Pd(II)-catalyzed C-H arylation of **3a**-(RS) with an *ortho*-substituted aryl iodide did not yield the product **6v**-(RS).



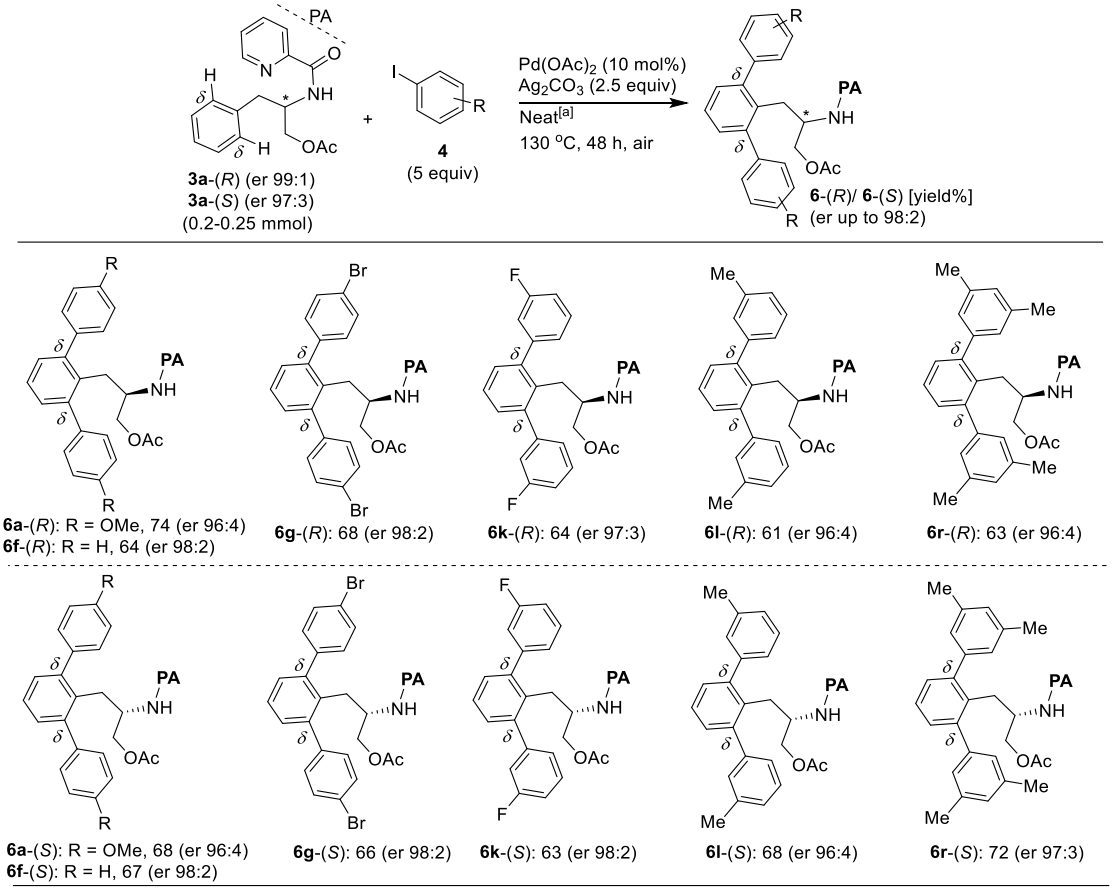
[a] The reaction was performed using *t*-AmylOH (2 mL) solvent in a RB flask. [b] Reactions done in a sealed/pressure tube filled with ambient air.

Scheme 3: Palladium(II) catalyzed *δ*-C-H arylation of phenylalaninols 3a-(*RS*).

We then focused our attention to perform the *ortho* C-H arylation of enantiopure phenylalaninol substrates and to synthesize enantiopure bis *δ*-C-H (*ortho*) arylated products (enantiopure phenylalaninol-based terphenyl derivatives). Scheme 4 shows the $Pd(OAc)_2$-catalyzed, Ag_2CO_3-promoted, picolinamide-directed *δ*-C-H (*ortho*) arylation of enantiopure phenylalaninol substrates **3a**-(R) and **3a**-(S) with aryl iodides. Initially, we treated the enantiopure phenylalaninol substrate **3a**-(R) possessing the picolinamide DG with aryl iodides

having a substituent at the para- or meta-position (e.g., OMe, Br, F, Me), PhI and a disubstituted aryl iodide in the presence of the $Pd(OAc)_2$ catalyst and Ag_2CO_3 additive under neat conditions at 130 ^oC for 48 h. These reactions gave the corresponding bis δ-C-H (*ortho*) arylated enantiopure products (Scheme 4). Accordingly, the enantiopure phenylalaninol-based terphenyl derivatives **6a**-(R) (74%, *er* 96:4), **6f**-(R) (64%, *er* 98:2), **6g**-(R) (68%, *er* 98:2), **6k**-(R) (64%, *er* 97:3), **6l**-(R) (61%, *er* 96:4) and **6r**-(R) (63%, *er* 96:4) were assembled.

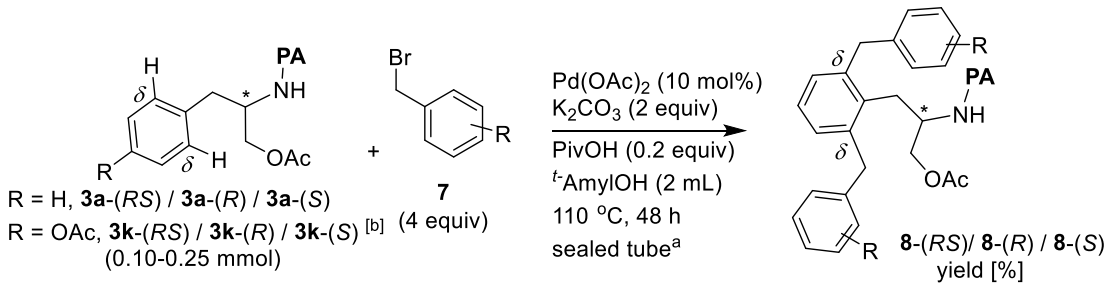
Similarly, we treated the enantiopure phenylalaninol substrate **3a**-(S) possessing the picolinamide DG with aryl iodides having a substituent at the para- or meta-position (e.g., OMe, Br, F, Me), PhI and a disubstituted aryl iodide in the presence of the $Pd(OAc)_2$ catalyst and Ag_2CO_3 additive under neat conditions at 130 ^oC for 48 h. These reactions also yielded the corresponding bis δ-C-H (*ortho*) arylated enantiopure products (Scheme 4). Accordingly, the enantiopure phenylalaninol-based terphenyl derivatives **6a**-(S) (68%, *er* 96:4), **6f**-(S) (67%, *er* 98:2), **6g**-(S) (66%, *er* 98:2), **6k**-(S) (63%, *er* 98:2), **6l**-(S) (68%, *er* 96:4) and **6r**-(S) (72%, *er* 97:3) have been assembled.



[a] Reactions done in a sealed/pressure tube filled with ambient air.

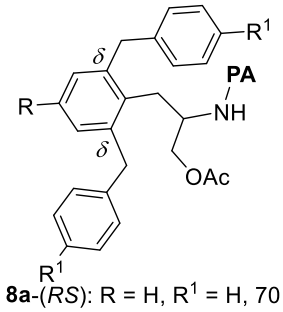
Scheme 4: Pd(II)-catalyzed δ-C-H arylation of phenylalaninols 3a-(*R*) and 3a-(*S*).

We then wished to extend the scope of the Pd(II)-catalyzed picolinamide-directed δ-C(sp^2)-H functionalization of phenylalaninol by attempting the alkylation, benzylation, bromination and iodination reactions. Scheme 5a shows the results of the δ-C(sp^2)-H benzylation of racemic and enantiopure phenylalaninol/tyrosinol substrates **3a**-(RS), **3a**-(R), **3a**-(S), **3k**-(RS), **3k**-(R) and **3k**-(S) with various benzyl bromides. The substrates **3a**-(RS) and **3k**-(RS) were treated with benzyl bromides having a substituent at the para- or meta-position (e.g., *t*-Bu, Cl and F) and benzyl bromide in the presence of the $Pd(OAc)_2$ catalyst, K_2CO_3 and PivOH additives in t-amylOH at 130 ^oC for 48 h in a sealed tube (under the conditions reported by Daugulis, Chen, and used by us earlier).[6b,d,9a] These reactions were found to afford the corresponding bis δ-C-H (*ortho*) benzylated phenylalaninols **8a-d**-(RS) and tyrosinols **8e-h**-(RS) (diarylmethane derivatives) in 60-79% yields. Subsequently, the enantiopure substrates **3a**-(R), **3a**-(S), **3k**-(R) and **3k**-(S) were treated with various benzyl bromides in the presence of the $Pd(OAc)_2$ catalyst, K_2CO_3 and PivOH additives in t-amylOH or toluene at 130 ^oC for 48 h in a sealed tube. These reactions afforded the corresponding bis δ-C-H (*ortho*) benzylated enantiopure phenylalaninols **8a**-(R) (56%, *er* 98:2), **8a**-(S) (76%, *er* 96:4), **8c**-(R) (64%, *er* 97:3), **8c**-(S) (65%, *er* 98:2) and tyrosinols **8e**-(R) (76%, *er* 97:3), **8e**-(S) (71%, *er* 98:2) (Scheme 5a).

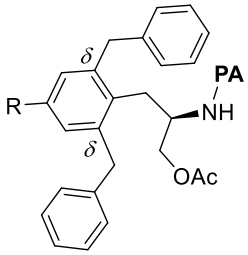


R = H, **3a**-(*RS*) / **3a**-(*R*) / **3a**-(*S*)
R = OAc, **3k**-(*RS*) / **3k**-(*R*) / **3k**-(*S*) [b]
(0.10-0.25 mmol)

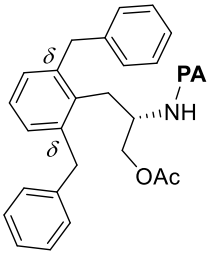
8-(*RS*)/ **8**-(*R*) / **8**-(*S*)
yield [%]



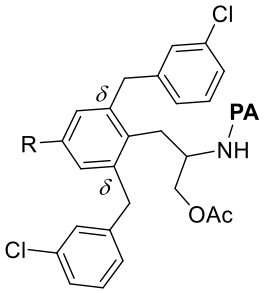
8a-(*RS*): R = H, R^1 = H, 70
8b-(*RS*): R = H, R^1 = ^{t}Bu, 66
8e-(*RS*): R = OAc, R^1 = H, 75
8f-(*RS*): R = OAc, R^1 = ^{t}Bu, 65
8d-(*RS*): R = H, R^1 = F, 60
8h-(*RS*): R = OAc, R^1 = Me, 71



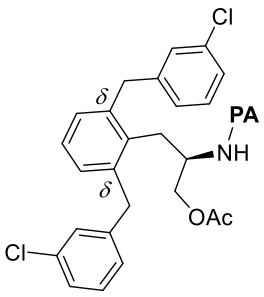
8a-(*R*): R = H, 56 (er 98:2)
8e-(*R*): R = OAc, 76 (er 97:3)



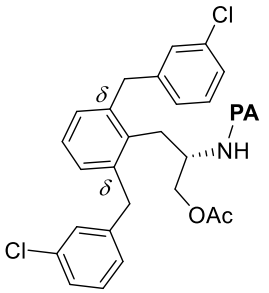
8a-(*S*): R = H, 76 (er 96:4)
8e-(*S*): R = OAc, 71 (er 98:2)



8c-(*RS*): R = H, 63
8g-(*RS*): R = OAc, 79



8c-(*R*): 64 (er 97:3)



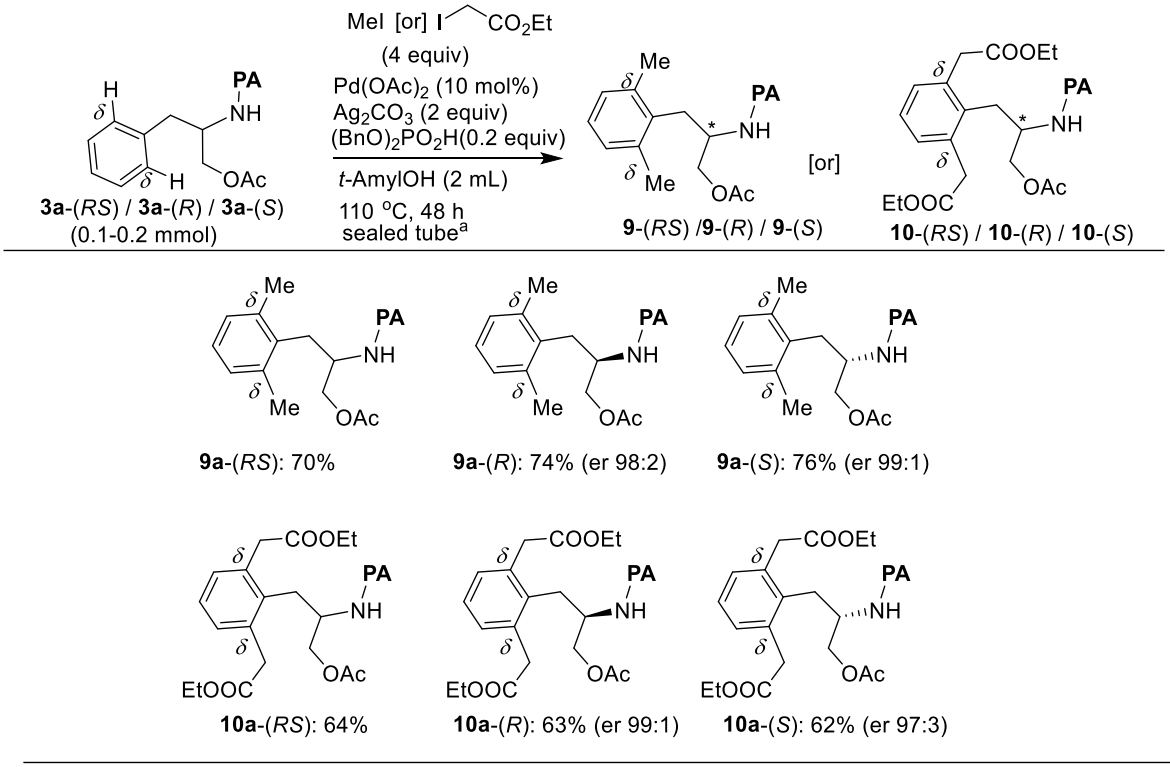
8c-(*S*): 65 (er 98:2)

[a] Reactions done in a sealed/pressure tube purged with nitrogen atm. [b] reaction was performed in toluene.

Scheme 5a: Pd(II)-catalyzed *δ*-C-H benzylation of phenylalaninols 3a-(*RS*), 3a-(*R*), 3a-(*S*) and 3k-(*RS*), 3k-(*R*), 3k-(*S*)

Next, we attempted the Pd(II)-catalyzed picolinamide-directed *δ*-C(sp^2)-H methylation of phenylalaninol substrates. Accordingly, the racemic and enantiopure substrates **3a**-(RS), **3a**-(R) and **3a**-(S) were treated with methyl iodide in the presence of the $Pd(OAc)_2$ catalyst, Ag_2CO_3 and $(BnO)_2PO_2H$ additives in *t*-amylOH at 110 °C for 48 h in a sealed tube (under the conditions reported by Chen).[6b,13a] These reactions were found to afford the corresponding bis *δ*-C-H (*ortho*) methylated racemic and enantiopure phenylalaninol derivatives **9a**-(RS) (70%), **9a**-(R) (74%, *er* 98:2) and **9a**-(S) (76%, *er* 99:1, Scheme 5b).

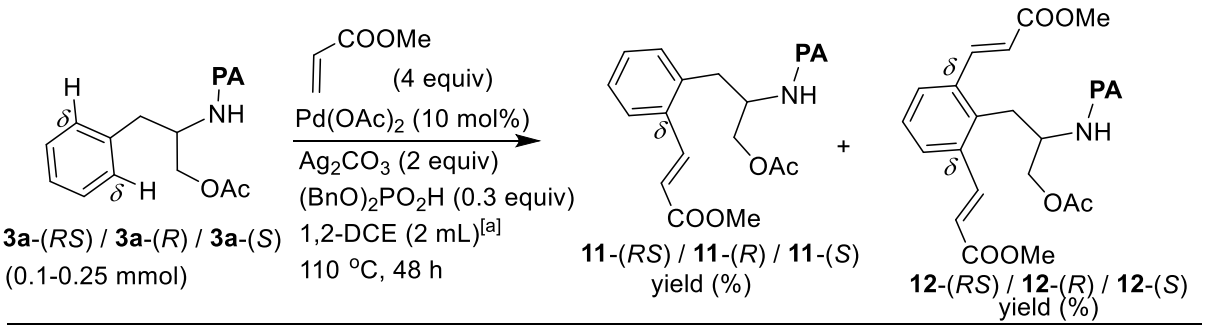
Then, the racemic and the enantiopure substrates **3a**-(RS), **3a**-(R) and **3a**-(S) were treated with ethyl iodoacetate in the presence of the $Pd(OAc)_2$ catalyst, Ag_2CO_3 and $(BnO)_2PO_2H$ additives in *t*-amylOH at 110 °C for 48 h in a sealed tube (under the conditions reported by Chen).[6b,13a] These reactions gave the corresponding bis δ-C-H (*ortho*)alkylated racemic and enantiopure phenylalaninol derivatives **10a**-(RS) (64%), **10a**-(R) (63%, *er* 99:1) and **10**-(S) (62%, *er* 97:3, Scheme 5b).

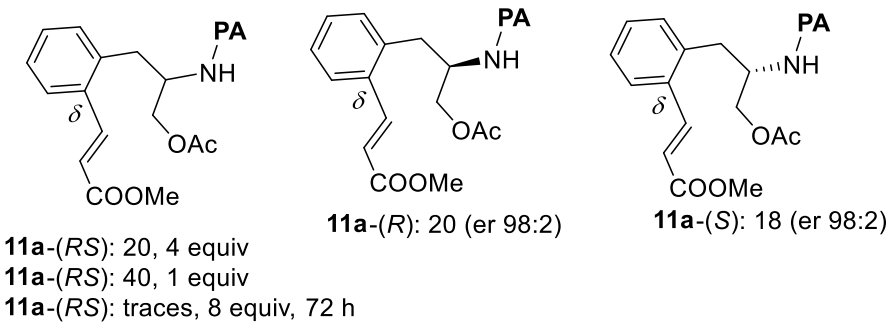


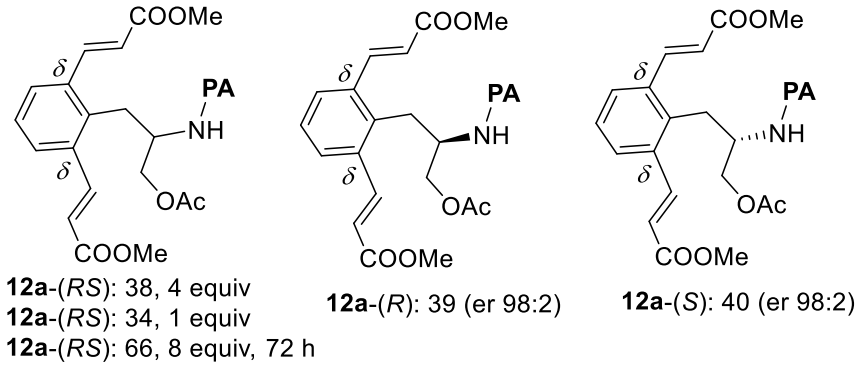
Scheme 5b: Pd(II)-catalyzed δ-C-H alkylation of phenylalaninols 3a-(*RS*), 3a-(*R*), 3a-(*S*)

Subsequently, the scope of the Pd(II)-catalyzed picolinamide-directed *ortho* δ-C(sp^2)-H functionalization of phenylalaninol was extended by attempting the δ-C(sp^2)-H alkenylation of phenylalaninol scaffolds. Scheme 6a shows the results of δ-C-H alkenylation of racemic and enantiopure phenylalaninol substrates **3a**-(RS), **3a**-(R) and **3a**-(S) with methyl acrylate. At first, the substrate **3a**-(RS) was treated with methyl acrylate (1 equiv) in the presence of the $Pd(OAc)_2$ catalyst, Ag_2CO_3 and $(BnO)_2PO_2H$ additives in 1,2-DCE at 110 °C for 48 h.[12f,g] This reaction afforded the mono δ-C-H (*ortho*) alkenylated compound (cinnamate derivative) **11a**-(RS) (40%) and bis δ-C-H (*ortho*) alkenylated phenylalaninol scaffold **12a**-(RS) (34%). The alkenylation of **3a**-(R) with 4 equiv of methyl acrylate also gave both the mono and bis alkenylated products **11a**-(RS) (20%) and **11a**-(RS) (38%). Notably, the alkenylation of **3a**-(R) with 8 equiv of methyl acrylate selectively gave the bis alkenylated product **12a**-(RS)

(66%). Subsequently, the enantiopure substrates **3a**-(R) and **3a**-(S) were treated with methyl acrylate (4 equiv) in the presence of the $Pd(OAc)_2$ catalyst, Ag_2CO_3 and $(BnO)_2PO_2H$ additives in 1,2-DCE at 110 ^oC for 48 h. These reactions afforded the corresponding mono δ-C-H alkenylated compounds **11a**-(R) (20%, *er* 98:2), **11a**-(S) (18%, *er* 98:2) and bis δ-C-H alkenylated enantiopure phenylalaninol scaffolds **12a**-(R) (39%, *er* 98:2), **12a**-(S) (40%, *er* 99:1, Scheme 6a).





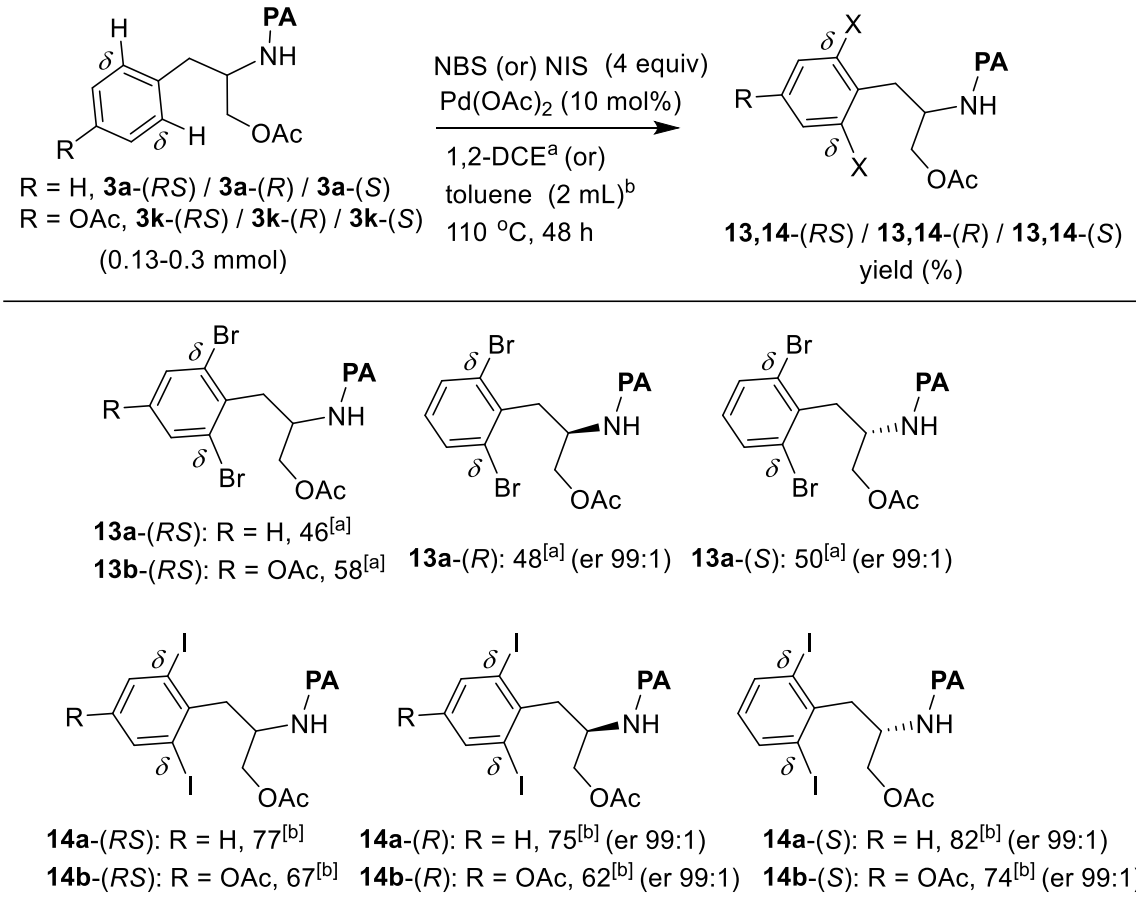


[a]Reactions done in a sealed/pressure tube purged with nitrogen atm.

Scheme 6a: Pd(II)-catalyzed δ-C-H alkenylation of phenylalaninols 3a-(*RS*), 3a-(*R*), 3a-(*S*)

Successively, we attempted the Pd(II)-catalyzed, picolinamide-directed δ-C-H (*ortho*) halogenation of phenylalaninol/tyrosinol substrates (Scheme 6b). Phenylalaninol **3a**-(RS) and tyrosinol **3k**-(RS) were subjected to the $Pd(OAc)_2$-catalyzed δ-C-H (*ortho*) bromination and iodination conditions using NBS or NIS (under the conditions reported by Jiang and used by

us earlier).[6a,d] These attempts yielded the corresponding bis δ-C-H (*ortho*) brominated phenylalaninol **13a**-(RS) (46%), tyrosinol **13b**-(RS) (58%) and iodinated phenylalaninol **14a**-(RS) (77%) and tyrosinol **14b**-(RS) (67%) Similarly, the enantiopure phenylalaninols **3a**-(R), **3a**-(S) and tyrosinols **3k**-(R) and **3k**-(S) were subjected to the $Pd(OAc)_2$-catalyzed δ-C-H bromination and iodination conditions. Accordingly, the corresponding δ-C-H brominated, enantiopure phenylalaninols **13a**-(R) (48%, *er* 99:1) and **13a**-(S) (50%, *er* 99:1) were assembled. Additionally, the corresponding δ-C-H iodinated enantiopure phenylalaninols **14a**-(R) (75%, *er* 99:1), **14a**-(S) (82%, *er* 99:1) and enantiopure tryosinols **14b**-(R) (62%, *er* 99:1), **14b**-(S) (74%, *er* 98:2) were assembled (Scheme 6b).



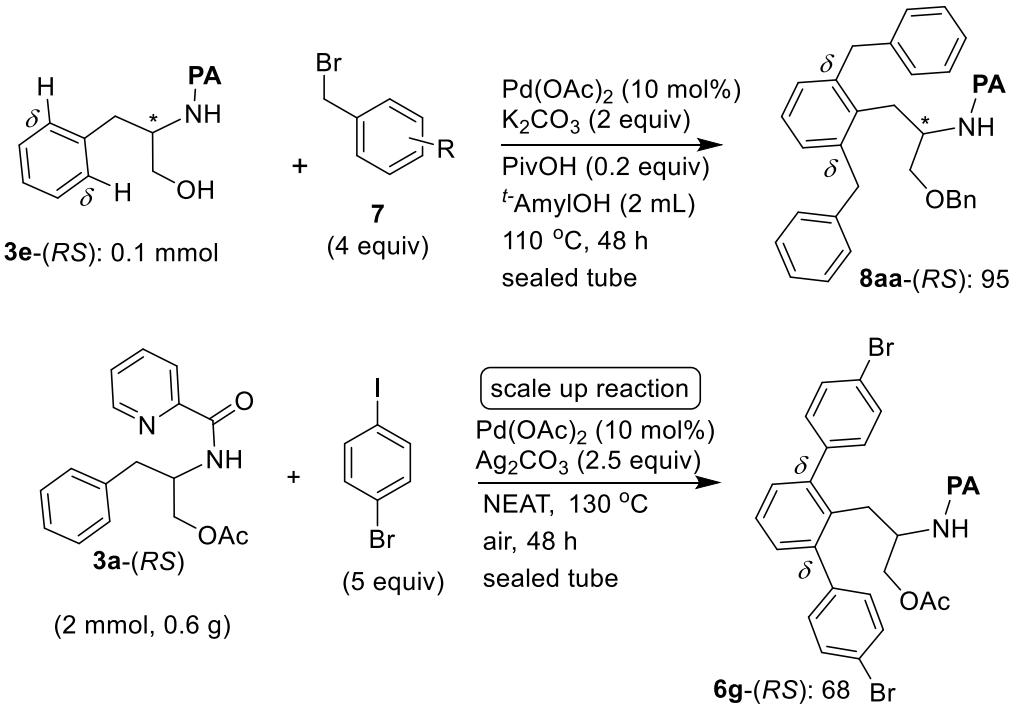
[a] Reactions done in a sealed/pressure tube filled with ambient air.[b] Reactions done in a RB flask.

Scheme 6b: Pd(II)-catalyzed δ-C-H halogenation of phenylalaninols 3a-(*RS*), 3a-(*R*), 3a-(*S*) and 3k-(*RS*), 3k-(*R*), 3k-(*S*)

The enantiopurity (*er*) of the δ-C-H functionalized phenylalaninol compounds **6a,f,g,k,l,r**-(R), **6a,f,g,k,l,r**-(S), **8a,c,e**-(R), **8a,c,e**-(S), **9a**-(R), **9a**-(S), **10a**-(R), **10a**-(S), **11a**-(R), **11a**-(S), **12a**-

(R), **12a**-(S), **13a**-(R), **13a**-(S), **14a,b**-(R) and **14a,b**-(S) were obtained from their corresponding HPLC analysis profiles (with reference to the HPLC analysis profiles of their corresponding racemic compounds **6a,f,g,k,l,r**-(RS), **8a,c,e**-(RS), **9a**-(RS), **10a**-(RS), **11a**-(RS), **12a**-(RS), **13a**-(RS) and **14a,b**-(RS), see the supporting information).

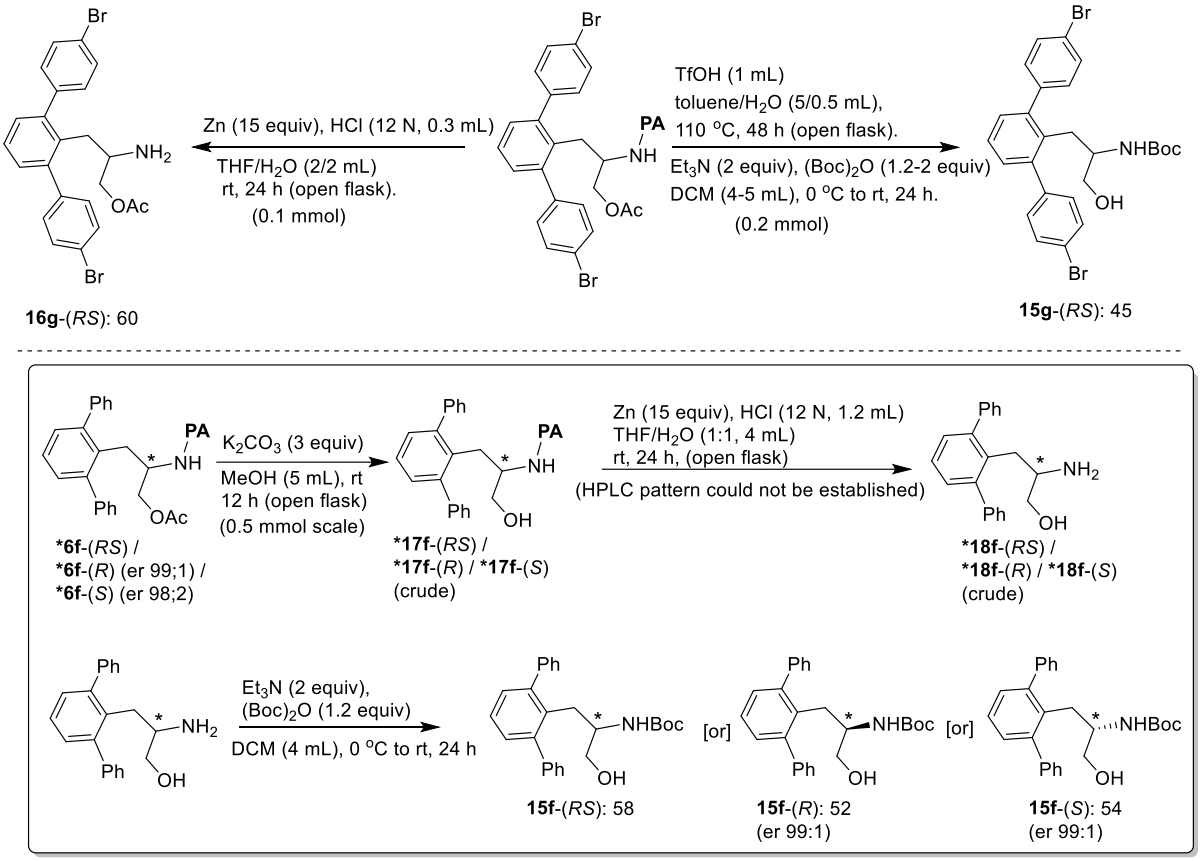
Then, we focused our attention to reveal the synthetic utility of this protocol comprising the Pd(II)-catalyzed, picolinamide-directed *ortho* δ-C-H functionalization of phenylalaninol motifs. At first, the Pd(II)-catalyzed C-H benzylation of phenylalaninol substrate **3e**-(RS) possessing the picolinamide DG and unprotected OH group was found to afford the product **8aa**-(RS) in 95% yield. Under the experimental condition, the OH group was also converted into the OBn in **8aa**-(RS) (Scheme 7a). It may be noted that earlier, the C-H arylation of **3e**-(RS) failed to afford the product **6ad**-(RS) (Scheme 2) but the benzylation of **3e**-(RS) is successful. Next, we performed the Pd(II)-catalyzed, picolinamide-directed δ-C(sp^2)-H arylation of substrate **3a**-(*RS*) with 1-bromo-4-iodobenzene in a slightly large-scale (Scheme 7a). This reaction yielded the bis δ-C-H (*ortho*) arylated phenylalaninol derivative **6g**-(RS) (phenylalaninol-based terphenyl derivative, possessing two bromo substituents in the newly introduced aryl groups) in 60% yield. The observed yield is comparable to the reaction, which was performed on a 0.2 mmol scale, which gave the product **6g**-(RS) in 60% yield (Scheme 3).



Scheme 7a: Benzylation of phenylalaninol with free OH group and scale up reaction

Next, we attempted the removal of the picolinamide DG from the δ-C(sp^2)-H arylated phenylalaninol substrates. Accordingly, a few trials were made to find out the suitable reaction conditions for removing the picolinamide DG. The bis (*ortho*) δ-C-H arylated compound **6g**-(RS) was sequentially treated with TfOH in a toluene/H_2O mixture at 110 ^oC for 48 h to afford the corresponding picolinoyl, we treated the compound **6g**-(RS) with Zn dust and HCl in THF/H_2O group removed and free amino alcohol derivative, which was then directly treated with $(Boc)_2O$. This process has led to the assembling of picolinamide DG-free, bis arylated NH-Boc protected phenylalaninol compound **15g**-(RS) (Scheme 7b). Then mixture at rt for 24 h in the air.[24] This reaction yielded the picolinamide DG-free phenylalaninol compound **16g**-(RS) (60%). While we were successful in removing the picolinamide DG but could not ascertain the HPLC analysis pattern for the racemic phenylalaninol compounds **15g**-(RS) and **16g**-(RS) under different columns and conditions. Thus, the corresponding picolinamide DG-free enantiopure phenylalaninol compounds were not prepared.

Subsequently, we tried the picolinamide DG removal using δ-C-H arylated racemic phenylalaninol compound **6f**-(RS). At first, the compound **6f**-(RS) was subjected to deacetylation conditions to afford the racemic phenylalaninol compound **17f**-(RS) possessing the picolinamide DG. The compound **17f**-(RS) was then treated with Zn dust and HCl in THF/H_2O mixture at rt for 24 h in the air. This reaction afforded the picolinamide DG-free phenylalaninol compound **18f**-(RS) (Scheme 7b). We successfully removed the picolinamide DG but again we could not ascertain the HPLC analysis pattern for the racemic compound **18f**-(RS) under different columns and conditions. The compound **18f**-(RS) was then treated with $(Boc)_2O$ to afford the bis arylated NH-Boc protected phenylalaninol compound **15f**-(RS). This time we could ascertain the HPLC analysis pattern for the bis arylated NH-Boc protected racemic compound **15f**-(RS). Having obtained the HPLC pattern for the compound **15f**-(RS), we then repeated the same sequence of deprotection reactions using enantiopure phenylalaninol compounds **6f**-(R) and **6f**-(S). Accordingly, the corresponding bis arylated NH-Boc protected enantiopure phenylalaninol compounds **15f**-(R) (52%, *er* 99:1) and **15f**-(S) (54%, *er* 99:1) were obtained and their enantiopurity was ascertained by HPLC analysis (Scheme 7b).

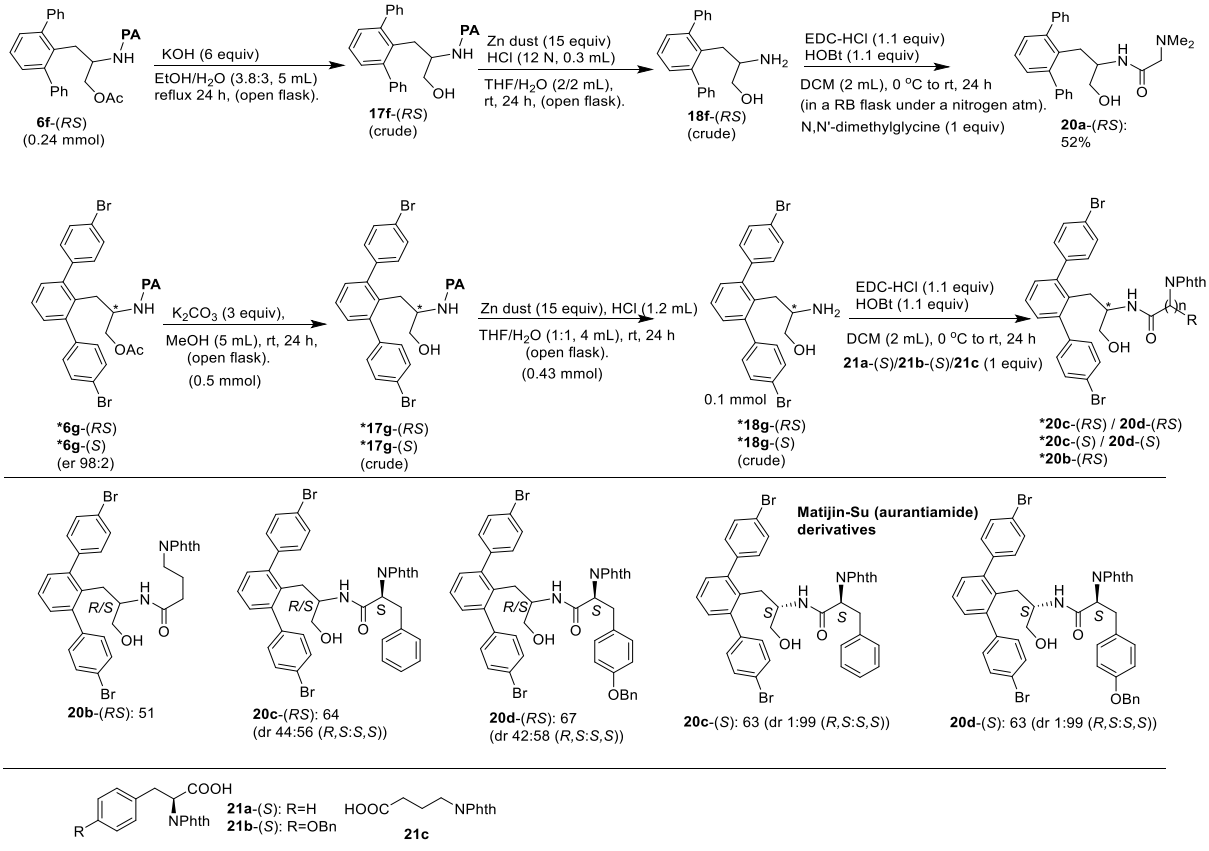


Scheme 7b: directing group removal transformations.

Finally, we wished to assemble some Matijin-Su (aurantiamide)[23] type derivatives using the bis *δ*-C-H (*ortho*) arylated phenylalaninol compounds. Towards this, at first, we assembled the picolinamide DG-free phenylalaninol compound **18f**-(RS) from **6f**-(RS) (Schemes 7a, 7b, and 8). Then, the compound **18f**-(RS) was subjected to the amide coupling reaction with *N*,*N*-dimethylglycine to afford the phenylalaninol and glycine coupled product **20a**-(RS) in 52% yield (Scheme 8). Next, we assembled the picolinamide DG-free, bis C-H arylated, racemic phenylalaninol **18g**-(RS) and enantiopure phenylalaninol **18g**-(S) from their corresponding *δ*-C-H arylated phenylalaninol derivatives **6g**-(RS) and **6g**-(S). The compound **18g**-(RS) was then subjected to the amide coupling reaction with *N*-Phthaloyl GABA (**21c**) or *N*-Phth-(S)-phenylalanine (**21a**) or *N*-Phth-(S)-tyrosine (**21b**) derivatives. Accordingly, the bis-C-H arylated phenylalaninol and *γ*-aminobutyric acid (GABA) coupled racemic compound **20b**-(RS) was obtained in 51% yield. Then, the aurantiamide type compounds including bis-C-H arylated, phenylalaninol-(S)-phenylalanine coupled product **20c**-(RS) (64%, *dr* 44:56, *R*,*S*:*S*,*S*) and phenylalaninol-(S)-tyrosine coupled product **20d**-(RS) (67%, *dr* 42:58, *R*,*S*:*S*,*S*) were obtained (Scheme 8). From HPLC analysis, the compounds **20c**-(RS) and **20d**-(RS) appear to

have a minor diastereomeric selection. This might have occurred during the separation or purification process.

Successively, the bis C-H arylated enantiopure phenylalaninol compound **18g**-(S) was then subjected to the amide coupling reaction with *N*-Phth-(S)-phenylalanine (**21a**) or *N*-Phth-(S)-tyrosine (**21b**) derivatives. Accordingly, the aurantiamide type compounds including bis C-H arylated enantiopure (S)-phenylalaninol and (S)-phenylalanine coupled product **20c**-(S) (63%, *dr* 1:99, *R,S*:*S,S*) and bis C-H arylated enantiopure (S)-phenylalaninol and (S)-tyrosine coupled product **20d**-(S) (63%, *dr* 1:99, *R,S*:*S,S*) were obtained (Scheme 8). The ratio of diastereomers of the compounds **20c**-(RS) (*dr* 44:56, *R,S*:*S,S*) and **20d**-(RS) (*dr* 42:58, *R,S*:*S,S*), which were prepared from the corresponding racemic **18g**-(RS) and enantiopure amino acids **21a,b** were ascertained from the HPLC analysis. Afterward, the diastereoselectivity of the enantiopure compounds **20c**-(S) (*dr* 1:99, *R,S*:*S,S*) and **20d**-(S) (*dr* 1:99, *R,S*:*S,S*), which were prepared from the corresponding enantiopure phenylalaninol **18g**-(S) and enantiopure amino acids **21a,b** were also ascertained from the HPLC analysis by comparing with the HPLC analysis profiles of **20c**-(RS) and **20d**-(RS).



Scheme 8: Synthetic transformations towards assembling of Matijin-Su (aurantiamide) derivatives using bis *δ*-C-H (*ortho*) arylated phenylalaninols.

The structures of all the C-H functionalized phenylalaninol compounds (Schemes 2-6 and Table 1) and related derivatives (Schemes 7 and 8) prepared in this work were ascertained by their NMR spectra. HPLC analysis of corresponding racemic and enantiopure samples was performed to obtain the enantiomeric ratio of enantiopure compounds. Additionally, the structure of a representative bis *δ*-C-H (*ortho*) arylated product (phenylalaninol-based terphenyl derivative) **6g**-(RS) was unequivocally confirmed by the single-crystal X-ray structure analysis (Figure 2).[25]

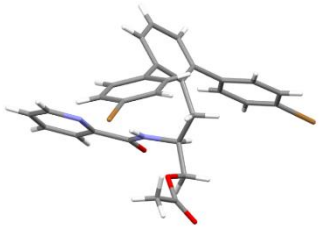
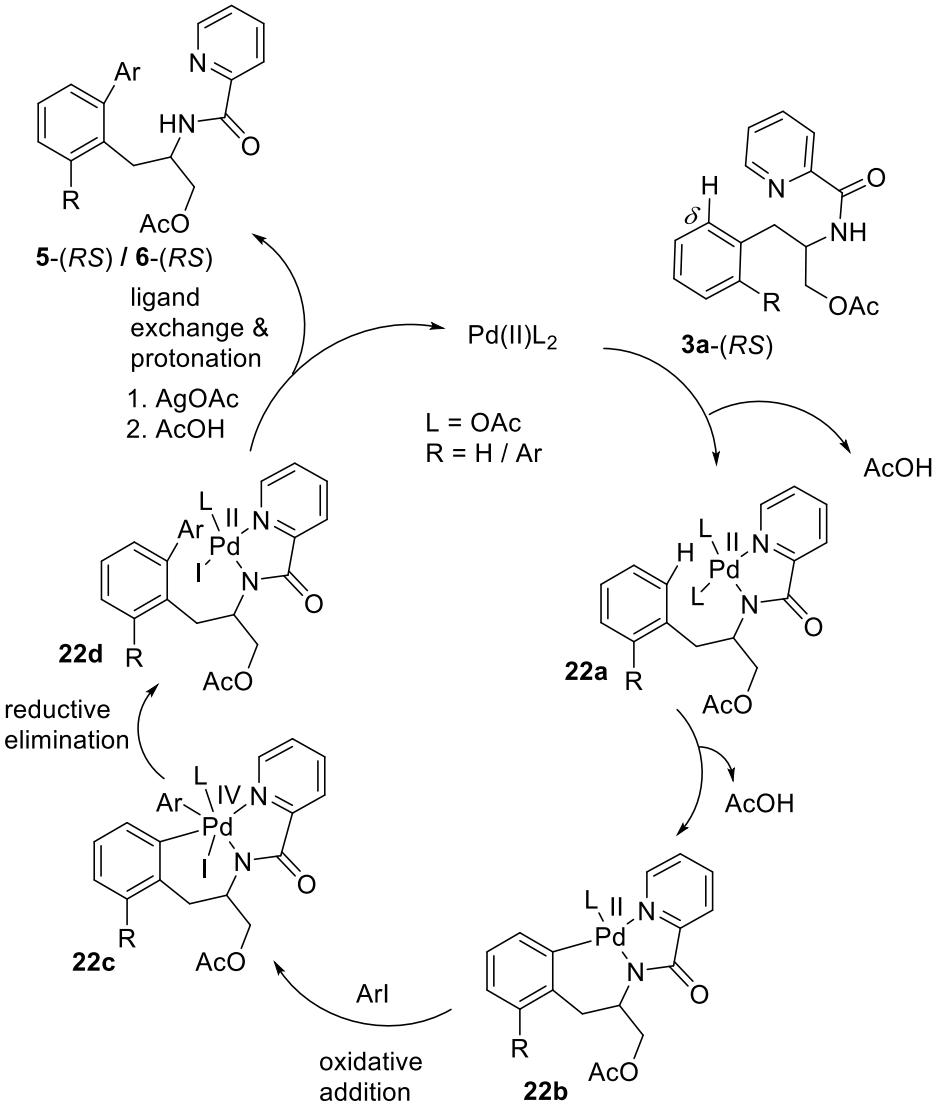


Figure 2: X-ray structure (capped and sticks model) of compound 6g-(*RS*).[25]

In general, the mechanism of the bidentate directing group picolinamide directing group-aided C–H activation and arylation of *γ*-C(sp^2)-H bonds of benzylamine[3,6a-e] or remote *δ*-C(sp^2)-H bonds of phenethylamine types of molecules is well documented.[3,4,5a,9-15] In concurrence with literature reports, the bidentate directing group picolinamide- directed intermolecular *δ*-C(sp^2)-H functionalization reaction of phenylalaninols discussed in this paper is believed to undergo *via* the well-documented Pd^{II}-Pd^{IV} catalytic cycle.[3,4,5a,9-15] Notably, a few recent reviews on remote C-H functionalization covered developments on the medium-sized metallacycle involved in C-H functionalization reactions.[4] In concurrence with the literature reports, a plausible mechanism for the picolinamide directing group-assisted Pd(II)-catalyzed arylation of the *δ*-C(sp^2)-H bond of phenylalaninol substrate **3a**-(RS) is proposed (Scheme 9). The coordination of the picolinamide directing group moiety in substrate **3a**-(RS) to the Pd(II) metal center is followed by concerted metalation deprotonation (CMD), affording the plausible six-membered Pd(II) species **22b**. Oxidative addition of the Pd(II) species **22b** with an aryl iodide then generates the Pd(IV) species **22c**. Subsequently, the Pd(IV) species **22c** undergoes reductive elimination to generate the new C–C bond in phenylalaninol derivative **22d**. Halide ion abstraction by halide ion scavenger (e.g., AgOAc) followed by the protonolysis of the Pd(II) intermediate **22d** gives the corresponding *δ*-C-H arylated product **5a**-(RS)/**6a**-(RS) and also the active Pd(II) catalyst is regenerated in the catalytic cycle (Scheme 9).



Scheme 9: Plausible mechanism in concurrence with the literature[3,4,5a,9-15] ·Pd(II)-catalyzed Picolinamide DG aided *δ*-C-H functionalization (arylation) of phenylalaninol substrate 3a-(*RS*).

In summary, we have shown the Pd(II)-catalyzed, picolinamide-directed C-H activation and functionalization of the remote *δ*-position[28-30] in racemic and enantiopure phenylalaninol (2-amino-3-phenylpropan-1-ol) scaffolds. Racemic and enantiopure phenylalaninol scaffolds possessing the picolinamide DG were subjected to the Pd(II)-catalyzed *δ*-C-H (*ortho*) arylation, alkylation, benzylation, alkenylation, bromination and iodination processes. These processes have led to the assembling of various *ortho* C-H arylated, alkylated, benzylated, alkenylated, brominated and iodinated, racemic and enantiopure phenylalaninol scaffolds. The C-H arylation and benzylation of phenylalaninols have led to the assembling of the corresponding bis C-H arylated phenylalaninols (phenylalaninol-based terphenyl or biaryl scaffolds)[26] and

bis C-H benzylated phenylalaninols (diarylmethane scaffolds).[27] Notably, the C-H arylation reaction of phenylalaninol was found to be efficient in neat condition. We have shown the removal of the picolinamide DG after performing the Pd(II)-catalyzed δ-C(sp^2)-H arylation of phenylalaninol substrates. Finally, we have shown the assembling of Matijin-Su (aurantiamide) type derivatives[23] using the bis δ-C-H (*ortho*) arylated phenylalaninol compounds prepared in this work. Considering the importance of phenylalaninols in the research areas of organic synthesis and medicinal chemistry, this work on assembling *ortho* C-H functionalized phenylalaninol scaffolds would be a valuable contribution to the expansion of the library of phenylalaninols. To the best of our knowledge, there is no literature report dealing with the Pd(II)-catalyzed picolinamide-directed DG-aided intermolecular functionalization of the remote δ-C(sp^2)-H bonds of phenylalaninol substrates. Thus, this work demonstrates the substrate scope development in remote C-H functionalization involving phenylalaninol motifs.

General: All reactions were done in an oven-dried round-bottom flask or sealed/pressure tubes in anhydrous solvents or neat condition under nitrogen or ambient air. TLC analyses were performed on silica gel or silica gel 60 F254 pre-coated plates and components were visualized with exposure to iodine vapour or by IR radiation under a UV lamp. The column chromatography purification was performed using silica gel (100-200 mesh) or neutral alumina (eluent = ethyl acetate:hexanes). ^{1}H NMR and ^{13}C{^{1}H} NMR spectra of samples have been recorded on a 400 and ~101 MHz spectrometer or 300 and ~76 MHz spectrometer or 500 and ~126 MHz spectrometer, respectively (using TMS as an internal standard). The HRMS data were obtained from the QTOF mass analyzer using the electrospray ionization (ESI) method. The IR spectra of samples have been recorded either using KBr pellets or in an appropriate solvent. For finding the specific rotations of enantiopure samples, the solutions were prepared in $CHCl_3$ solvent, polarimeter data were recorded at 589 nm wavelength using 100 mm cell length, concentration (c) taken as g/100 mL. HPLC analysis was carried out on isolated samples. Isolated yields were given and yields were not optimized. Sometimes there is some variation in yields and enantiomeric ratio for the corresponding racemic/enantiopure pairs; this is perhaps due to the collection of major parts of pure fractions from the column chromatography based on the TLC and also may be due to inadvertent handling/processing errors of samples. The crude substrates **3h**-(RS) and **3j**-(RS) was used in the screening reaction (Scheme 2) and their characterization data is not presented. The arylation reactions shown in Schemes 3 and 4 were performed under neat conditions by using aryl iodides as the reaction

medium. Most of the aryl iodides are liquid at room temperature. The mp of some of the aryl iodides which are solid at rt are; 4-iodoanisole = 50-53 ^{o}C, 4-iodotoluene = 33-35 ^{o}C, 1-bromo-4-iodobenzene = 89-91 ^{o}C; methyl 4-iodobenzoate = 112-116 ^{o}C; 1-chloro-4-iodobenzene = 53-54 ^{o}C; 1-iodo-4-nitrobenzene = 171-173 ^{o}C.

General procedure for the preparation of phenylalaninol carboxamide linked with directing group (Procedure A): An appropriate amount of (directing group) carboxylic acid (1-10 mmol), *N*,*N*'-dicyclohexylcarbodiimide (1.1 equiv), 1-hydroxybenzotriazole hydrate (1.1 equiv) in DCM (2-20 mL) were stirred for 1 h at 0 ^{o}C under a nitrogen atm. Next, an appropriate amount of phenylalaninol (1 equiv) was added to the above mixture and stirred for 24 h at rt. Then, the resulting solution was subjected to an aq. workup and washed with aq. sodium bicarbonate solution (two times). Then, the resulting crude reaction mixture was purified using silica gel column chromatography to obtain corresponding phenylalaninol carboxamide linked with directing group (having free OH group), which as then used in next step (Procedure B).

Step 2. General procedure for the acetylation of the free alcohol group in phenylalaninol carboxamide (linked with the directing group) (Procedure B): An appropriate amount of phenylalaninol carboxamide (linked with directing group and having free OH group) prepared in step 1 (Procedure A), was dissolved in dry DMF followed by the addition of 4-(dimethylamino)pyridine (0.1 equiv) and acetic anhydride (1.1 equiv) and the resulting reaction mixture was stirred overnight at rt under a nitrogen atm. Then, the resulting solution was diluted with water and extracted with EtOAc, and the combined organic phase was washed with brine solution. The resulting solution was then concentrated and purified on silica gel column chromatography (eluent = EtOAc:hexanes) to give the corresponding OH group acetylated phenylalaninol carboxamide (linked with the directing group).

General procedure for the Pd(II)-catalyzed, directing group-aided *ortho* C-H arylation of phenylalaninol carboxamide (Procedure C): A mixture of an appropriate phenylalaninol carboxamide possessing a directing group (0.1-0.3 mmol, 1 equiv), an appropriate aryl iodide (5 equiv), $Pd(OAc)_2$ (10 mol%) and Ag_2CO_3 (2.5 equiv) was added in a sealed/pressure tube capped with silicone septum/Teflon which was heated at 100-130 ^{o}C for 24-48 h (the tube was filled with ambient air). After the reaction period, purification of the reaction mixture by column chromatography on silica gel (eluent = EtOAc:hexanes) gave the corresponding *ortho* C-H arylated phenylalaninol carboxamide (see the Tables/Schemes for specific entry).

General procedure for the Pd(II)-catalyzed *ortho* C-H benzylation of phenylalaninol carboxamide (Procedure D): A mixture of an appropriate phenylalaninol carboxamide possessing picolinamide DG (0.15-0.25 mmol, 1 equiv), an appropriate benzyl bromide (4

equiv), $Pd(OAc)_2$ (10 mol%), K_2CO_3 (2 equiv) and PivOH (0.2 equiv) in anhydrous t-amylOH (2 mL) was heated in a sealed tube capped with Teflon cap at 110 ^oC for 48 h (the tube was purged with 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 silica gel (eluent = EtOAc:hexanes) gave the corresponding *ortho* C-H benzylated phenylalaninol carboxamide (see the Tables/Schemes for specific entry).

General procedure for the Pd(II)-catalyzed *ortho* C-H alkylation of phenylalaninol carboxamide (Procedure E): A mixture of an appropriate phenylalaninol carboxamide possessing picolinamide DG (0.10-0.20 mmol, 1 equiv), an appropriate alkyl iodide (4 equiv), $Pd(OAc)_2$ (10 mol%), Ag_2CO_3 (2 equiv) and $(BnO)_2PO_2H$ (0.2 equiv) in anhydrous t-amylOH (2 mL) was heated in a sealed tube capped with Teflon cap at 110 ^oC for 48 h (the tube was purged with 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 silica gel (eluent = EtOAc:hexanes) gave the corresponding *ortho* C-H alkylated phenylalaninol carboxamide (see the Tables/Schemes for specific entry).

General procedure for the Pd(II)-catalyzed *ortho* C-H olefination of phenylalaninol carboxamide (procedure F): A mixture of an appropriate phenylalaninol carboxamide possessing picolinamide DG (0.25 mmol, 1 equiv), an appropriate methyl acrylate (0.8 mmol, 4 equiv), $Pd(OAc)_2$ (10 mol%), Ag_2CO_3 (2 equiv) and $(BnO)_2PO_2H$ (0.3 equiv) in anhydrous 1,2-DCE (2 mL) was heated in a sealed tube capped with Teflon cap at 110 ^0C for 48 h (the tube was purged with 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 silica gel (eluent = EtOAc:hexanes) gave the corresponding *ortho* C-H olefinated phenylalaninol carboxamide (see the Tables/Schemes for specific entry).

General procedure for the Pd(II)-catalyzed *ortho* C-H bromination of phenylalaninol carboxamide (Procedure G): A mixture of phenylalaninol carboxamide possessing picolinamide DG (0.1-0.3 mmol, 1 equiv), *N*-bromosuccinimide (4 equiv), $Pd(OAc)_2$ (10 mol%) in anhydrous 1,2-DCE (2 mL) was heated in a sealed tube capped with Teflon cap at 110 ^0C for 48 h (the tube was filled with ambient air). After the reaction period, the reaction mixture was concentrated in a vacuum and purification of the resulting reaction mixture by column chromatography on silica gel (eluent = EtOAc:hexanes) gave the corresponding *ortho* C-H brominated phenylalaninol carboxamide (see the Tables/Schemes for specific entry).

General procedure for the Pd(II)-catalyzed *ortho* C-H iodination of phenylalaninol carboxamide (Procedure H): A mixture of a phenylalaninol carboxamide (0.1-0.2 mmol, 1equiv), *N*-iodosuccinimide (0.4-0.8 mmol, 4 equiv), $Pd(OAc)_2$ (10 mol%) in anhydrous 1,2-toluene (2 mL) was heated in a round bottom flask (fitted with a condenser) at 110 ^oC for 48 h under the open air. After the reaction period, the reaction mixture was concentrated in a vacuum and purification of the resulting reaction mixture by column chromatography on silica gel (eluent = EtOAc:hexanes) gave the corresponding *ortho* C-H iodinated phenylalaninol carboxamide (see the Tables/Schemes for specific entry).

General procedure for the deacetylation of (OAc group) phenylalaninol carboxamide (Procedure I): An appropriate arylated phenylalaninol carboxamide with OAc group (0.5 mmol) was taken in a round bottom flask containing MeOH (5 mL). To this solution K_2CO_3 (3 equiv) was added and the reaction mixture was stirred was 24 h in the open air. After the reaction was over, the reaction mixture was concentrated in a vacuum and then diluted with ethyl acetate and washed with sodium bicarbonate solution and this resulting solution was dried over anhydrous sodium sulfate. The resulting solution was then concentrated and used for the next step without further purification.

General procedure for the deacetylation of (OAc group) phenylalaninol carboxamide (Procedure J): An appropriate arylated phenylalaninol carboxamide with OAc group (0.24 mmol) was taken in a round bottom flask containing EtOH/H_2O (ratio = 3.8:3.0, 5 mL). To this solution, KOH (6 equiv) was added and the reaction mixture was refluxed for 24 h in the open air. After the reaction was over, the reaction mixture was acidified with 1 N HCl solution, extracted with DCM and this resulting solution was dried over anhydrous sodium sulfate. The resulting solution was then concentrated and used for the next step without further purification.

A typical procedure for the removal of the picolinoyl group after C-H arylation (Procedure K): An appropriate *ortho* C-H arylated phenylalaninol carboxamide possessing picolinamide DG (0.20 mmol) was taken in a round bottom flask, in which trifluoromethanesulfonic acid (1 mL), and toluene:H_2O (5:0.5 mL) were added. The reaction mixture was stirred at 110 ^oC for 48 h in the open air. After the reaction period reaction mixture was cooled to rt and quenched adding a saturated solution of Na_2CO_3 (10 mL) slowly. The aq. phase was extracted with ethyl acetate, the reaction mixture was concentrated in a vacuum and used as such for the next step.

A typical procedure for the removal of the picolinoyl group after C-H arylation (Procedure L): To an appropriate *ortho* C-H arylated phenylalaninol carboxamide possessing picolinamide DG (0.10 mmol, 1.0 equiv) dissolved in H_2O/THF (ratio = 1:1, 4 mL) HCl (12

N, 0.3 mL) was added, and the mixture was stirred for 15 min at rt. Zinc dust (15 equiv) was then added in three portions and the mixture was stirred at rt. After 24 h, the reaction was filtered through a celite plug. The filtrate was transferred into a separating funnel with 2 M NaOH (50 mL) and extracted with DCM. Then, the resulting crude reaction mixture was purified using silica gel column chromatography to obtain the corresponding picolinoyl group removed phenylalaninol.

General procedure for the Boc protection of free NH_2 group after removal of picolinoyl group (Procedure M): A RB flask containing a mixture of an appropriate phenylalaninol derivative (0.2-0.5 mmol) (obtained in procedure K or L), Et_3N (2 equiv) and Boc_2O (2 equiv) in DCM (4-5 mL) was stirred for 24 h at rt a nitrogen atm. Then, the resulting solution was then subjected to a brine workup. Then, the resulting crude reaction mixture was purified using silica gel column chromatography to obtain the corresponding *N*-Boc-protected phenylalaninol derivative.

General procedure for the preparation of coupling *N*-protected amino acid with the NH_2 group of phenylalaninol derivative (Procedure N): An appropriate amount of *N*-protected amino acid (0.1 mmol), *N*-ethyl-N′-(3-dimethylaminopropyl)carbodiimide hydrochloride (1.1 equiv), 1-hydroxybenzotriazole hydrate (1.1 equiv) in DCM (2 mL) were stirred (in an RB flask) for 1 h at 0 ^oC under a nitrogen atm. Then an appropriate amount of free NH_2 group possessing phenylalaninol derivative (1 equiv) was added to the above mixture and stirred for 24 h at rt. Then, the resulting solution was subjected to an aq. workup and washed with aq. sodium bicarbonate solution. Then, the resulting crude reaction mixture was purified using silica gel column chromatography to obtain the corresponding product of *N*-protected amino acid coupled with the NH_2 group of phenylalaninol derivative.

General procedure for the synthesis of phenylalaninol from phenylalanine (amino acid) (Procedure O): To a suspension of phenylalanine (10 mmol, 1 equiv) and $NaBH_4$ (2.5 equiv) in dry THF (20 mL) at 0 °C, a solution of I_2 (1 equiv) in dry THF was added dropwise under a nitrogen atmosphere. The reaction mixture was refluxed for 24 h and then cooled to rt. Methanol was added dropwise until the solution became clear. After stirring for 1 h at rt the solvent was removed under reduced pressure. To the residue was added 20% aqueous KOH (30 mL) and the mixture was stirred for 4 h at rt. The aqueous phase was extracted with CH_2Cl_2 and washed with water. The combined organic layers were dried over anhydrous Na_2SO_4 and evaporated under a reduced pressure to give the corresponding phenylalaninol as a colourless oil (then procedures A and B were used to obtain the required picolinamide DG linked substrate).

General procedure for *O*-silylation of OH-free phenylalaninol linked with picolinamide (Procedure P): To a solution of OH-free phenylalaninol linked with picolinamide (0.67 mmol) in DCM (4 mL), imidazole (2 equiv), DMAP (0.1 equiv) and TBSCl (1.2 equiv) were added and the resulting solution was stirred at rt for 24 h under a nitrogen atmosphere and then the solution was quenched with saturated $NaHCO_3$ solution. The organic layers were washed with $NaHCO_3$ and brine solution, and evaporated, then the resulting crude material was purified on a silica gel column (eluent = EtOAc:hexanes) to give the corresponding O-TBS protected, phenylalaninol derivative possessing the picolinamide DG.

General procedure for *O*-benzylation OH-free phenylalaninol linked with picolinamide (Procedure Q): To a solution of OH-free phenylalaninol linked with picolinamide (0.6 mmol) in dry DMF (2 mL), NaH (1.2 equiv) and BnBr (1.2 equiv) were added and the resulting solution was stirred at rt under nitrogen atmosphere for 24 h. Then, the solution was quenched with brine solution, the resulting aqueous phase was extracted with ethyl acetate and dried over anhydrous sodium sulfate. Then, the resulting crude mixture was evaporated and purified on silica gel column chromatography (eluent = EtOAc:hexanes) to give the corresponding O-benzyl protected, phenylalaninol derivative possessing the picolinamide DG.

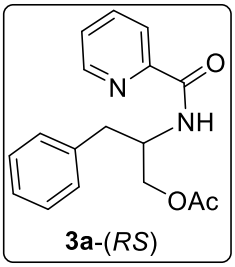
General procedure for the preparation compounds 3k-(RS)/3k-(R)/3k-(S) (Procedures R, S, T and U): Procedure R. To a solution of tyrosine methyl ester hydrochloride salt (10 mmol) in DCM (20 mL), imidazole (2 equiv), DMAP (0.1 equiv) and TBSCl (1.2 equiv) were added and the resulting solution was stirred at rt for 48 h under a nitrogen atmosphere and then the reaction was quenched with saturated $NaHCO_3$ solution. The organic layers were washed with $NaHCO_3$, brine solution and dried over anhydrous sodium sulphate and then subjected to evaporation to give the corresponding methyl 2-amino-3-(4-((*tert*-butyldimethylsilyl)oxy)phenyl)propanoate which was then used as such for next step.

Procedure S. An appropriate amount of picolinic acid (10 mmol), 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide (1.1 equiv), 1-hydroxybenzotriazole hydrate (1.1 equiv) in DCM (20 mL) were stirred at 0 ^oC for 1 h under a nitrogen atm. Next, an appropriate amount of methyl 2-amino-3-(4-((*tert*-butyldimethylsilyl)oxy)phenyl)propanoate (1 equiv) was added to the above mixture and stirred at rt for 24 h. Then, the resulting solution was subjected to an aq. workup and washed with aq. sodium bicarbonate solution. Then, the resulting crude reaction mixture was purified using silica gel column chromatography (eluent = EtOAc:hexanes) to obtain methyl 3-(4-((*tert*-butyldimethylsilyl)oxy)phenyl)-2-(picolinamido)propanoate (which was then used in the next step and preparation of this compound is known in the literature.[13d]

Procedure T. To an appropriate amount of methyl 3-(4-((*tert*-butyldimethylsilyl)oxy)phenyl)-2-(picolinamido)propanoate (3 mmol) dissolved in dry THF (6 mL), $NaBH_4$ (5 equiv) was added and then the resulting solution was refluxed for 15 min at 65 °C under a nitrogen atm. Methanol (3 mL) was then added and stirring was maintained for a further period of 1 h. After that, the solvent was removed under a vacuum, leaving a white paste, which was dissolved by the addition of 1 N aq. HCl. The solution was stirred for 2 h, neutralized with 2 M NaOH, and extracted with DCM to afford *N*-(1-hydroxy-3-(4-hydroxyphenyl)propan-2-yl)picolinamide (which was then used as such in the next step).

Procedure U. An appropriate amount of *N*-(1-hydroxy-3-(4-hydroxyphenyl)propan-2-yl)picolinamide prepared in procedure T was dissolved in dry DMF (6 mL) followed by the addition of 4-(dimethylamino)pyridine (0.1 equiv) and acetic anhydride (1.1 equiv), and the resulting reaction mixture was stirred overnight at rt under a nitrogen atmosphere. Then, the resulting solution was diluted with water and extracted with ethyl acetate, and combined organic phase was washed with brine solution. The resulting solution was then concentrated and purified on silica gel column chromatography (eluent = EtOAc:hexanes) to give the corresponding **3k**-(RS)/**3k**-(R)/**3k**-(S).

3-Phenyl-2-(picolinamido)propyl acetate (3a-(RS)):



3a-(*RS*)

Compound **3a**-(RS) was obtained from procedures A and B after purification by column chromatography on silica gel (EtOAc:hexanes = 40:60) as a colourless solid (1.75 g, 60%, 10 mmol scale). R_f (EtOAc/hexanes = 40:60) 0.5. mp: 72-74 °C.

IR (DCM): 3342, 1742, 1522 cm^{-1}.

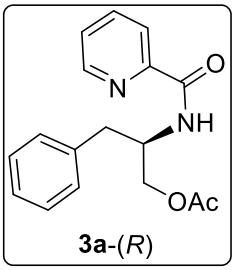
^1H NMR (400 MHz, $CDCl_3$): δ_H 8.56-8.55 (1H, m), 8.22 (1H, d, J = 8.8 Hz), 8.17 (1H, d, J = 7.8 Hz), 7.84 (1H, td, J_1 = 7.7 Hz, J_2 = 1.6 Hz), 7.44-7.41 (1H, m), 7.31-7.20 (5H, m), 4.66-4.61 (1H, m), 4.17 (2H, d, J = 4.8 Hz), 3.04 (1H, dd, J_1 = 13.8 Hz, J_2 = 6.7 Hz), 2.95 (1H, dd, J_1 = 13.8 Hz, J_2 = 7.8 Hz), 2.10 (3H, s).

$^{13}C\{^1H\}$ NMR (~101 MHz, $CDCl_3$): δ_C 170.9, 164.0, 149.6, 148.1, 137.4, 137.1, 129.3, 128.6, 126.7, 126.3, 122.3, 64.8, 49.5, 37.8, 20.9.

HRMS (ESI): *m/z* $(M + H)^+$ calcd for $C_{17}H_{19}N_2O_3$: 299.1396 found: 299.1382.

The HPLC of compound **3a**-(RS) was determined by using the Daicel Chiralpak IA column, hexane/*i*-PrOH 85:15, flow rate 1.0 mL/min, UV detection at 254 nm, t_R = 12.92 min, t_S = 12.11 min.

(R)-3-Phenyl-2-(picolinamido)propyl acetate (3a-(R)):



3a-(*R*)

Compound **3a**-(R) was obtained from procedures A and B after purification by column chromatography on silica gel (EtOAc:hexanes = 40:60) as a colourless solid (923 mg, 62%, 5 mmol scale). R_f (EtOAc/hexanes = 40:60) 0.5. mp: 70-72 ºC.

IR (DCM): 3385, 1741, 1522 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ_H 8.55 (1H, d, J = 4.1 Hz), 8.24 (1H, d, J = 8.6 Hz), 8.17 (1H, d, J = 7.8 Hz), 7.83 (1H, t, J = 7.6 Hz), 7.43-7.40 (1H, m), 7.31-7.20 (5H, m), 4.68-4.60 (1H, m), 4.17 (2H, d, J = 4.3 Hz), 3.04 (1H, dd, J_1 = 13.9 Hz, J_2 = 6.6 Hz), 2.95 (1H, dd, J_1 = 13.7 Hz, J_2 = 7.7 Hz), 2.09 (3H, s).

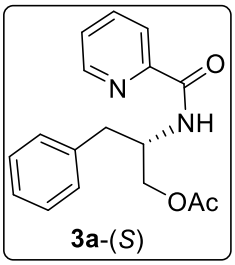
$^{13}C\{^1H\}$ NMR (~101 MHz, $CDCl_3$): δ_C 170.8, 163.9, 149.5, 148.0, 137.3, 137.0, 129.2, 128.5, 126.6, 126.2, 122.2, 64.7, 49.4, 37.6, 20.8.

HRMS (ESI): *m/z* $(M + H)^+$ calcd for $C_{17}H_{19}N_2O_3$: 299.1396 found: 299.1389.

$(\alpha)^{25}_D$ = 30.0 (c = 0.02 g/mL, $CHCl_3$).

The enantiomeric ratio (*er* 99:1) of compound **3a**-(R) was determined by using the Daicel Chiralpak IA column, hexane/*i*-PrOH 85:15, flow rate 1.0 mL/min, UV detection at 254 nm, t_R = 12.83 min, t_S = 11.87.

(S)-3-Phenyl-2-(picolinamido)propyl acetate (3a-(S)):



3a-(*S*)

Compound **3a**-(S) was obtained from procedures A and B after purification by column chromatography on silica gel (EtOAc:hexanes = 40:60) as a colourless solid (730 mg, 61%, 4 mmol scale). R_f (EtOAc/hexanes = 40:60) 0.5. mp: 70-72 ºC.

IR (DCM): 3390, 1741, 1522 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ_H 8.56-8.55 (1H, m), 8.23 (1H, d, J = 8.8 Hz), 8.18 (1H, d, J = 7.8 Hz), 7.84 (1H, td, J_1 = 7.7 Hz, J_2 = 1.7 Hz), 7.44-7.41 (1H, m), 7.31-7.20 (5H, m), 4.67-4.61 (1H, m), 4.17 (2H, d, J = 4.8 Hz), 3.04 (1H, dd, J_1 = 13.7 Hz, J_2 = 6.5 Hz), 2.95 (1H, dd, J_1 = 13.7 Hz, J_2 = 7.8 Hz), 2.10 (3H, s).

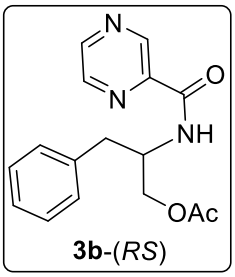
$^{13}C\{^1H\}$ NMR (~101 MHz, $CDCl_3$): δ_C 171.0, 164.0, 149.6, 148.1, 137.4, 137.1, 129.3, 128.6, 126.8, 126.3, 122.3, 64.8, 49.5, 37.7, 20.9.

HRMS (ESI): *m/z* $(M + H)^+$ calcd for $C_{17}H_{19}N_2O_3$: 299.1396 found: 299.1402.

(a)$^{25}_D$ = -26.0 (c = 0.02 g/mL, $CHCl_3$).

The enantiomeric ratio (*er* 97:3) of compound **3a**-(S) was determined by using the Daicel Chiralpak IA column, hexane/*i*-PrOH 85:15, flow rate 1.0 mL/min, UV detection at 254 nm, t_R = - min, t_S = 12.15 min.

3-Phenyl-2-(pyrazine-2-carboxamido)propyl acetate (3b-(RS)):



3b-(*RS*)

Compound **3b**-(RS) was obtained after procedures A and B by column chromatography on silica gel (EtOAc:hexanes = 40:60) as a colourless solid (141 mg, 47%, 1 mmol scale). R_f (EtOAc/hexanes = 40:60) 0.4. mp: 123-125 ºC.

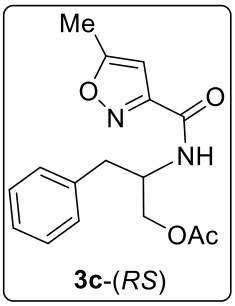
IR (DCM): 3357, 1737, 1522 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ_H 9.38 (1H, d, J = 1.4 Hz), 8.75 (1H, d, J = 2.5 Hz), 8.54-8.53 (1H, m), 7.98 (1H, d, J = 8.8 Hz), 7.32-7.28 (2H, m), 7.25-7.20 (3H, m), 4.70-4.61 (1H, m), 4.18 (2H, d, J = 4.9 Hz), 3.04 (1H, dd, J_1 = 13.8 Hz, J_2 = 6.6 Hz), 2.96 (1H, dd, J_1 = 13.8 Hz, J_2 = 7.6 Hz), 2.10 (3H, s).

$^{13}C\{^1H\}$ NMR (~101 MHz, $CDCl_3$): δ_C 170.8, 162.6, 147.3, 144.3, 144.1, 142.5, 136.7, 129.1, 128.6, 126.8, 64.6, 49.5, 37.5, 20.8.

HRMS (ESI): *m/z* $(M + Na)^+$ calcd for $C_{16}H_{17}N_3NaO_3$: 322.1168 found: 322.1178.

2-(5-Methylisoxazole-3-carboxamido)-3-phenylpropyl acetate (3c-(RS)):



3c-(*RS*)

Compound **3c**-(RS) was obtained from procedures A and B by column chromatography on silica gel (EtOAc:hexanes = 40:60) as a colourless solid (190 mg, 63%, 1 mmol scale). R_f (EtOAc/hexanes = 40:60) 0.4. mp: 114-116 ºC.

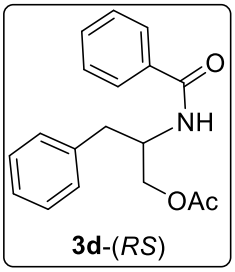
IR (DCM): 3340, 1734, 1539 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ_H 7.31-7.7.27 (2H, m), 7.23-7.20 (3H, m), 7.04 (1H, d, J = 8.7 Hz), 6.41 (1H, s), 4.64-4.56 (1H, m), 4.16 (1H, dd, J_1 = 11.4 Hz, J_2 = 4.2 Hz), 4.11 (1H, dd, J_1 = 11.6 Hz, J_2 = 5.4 Hz), 2.98 (1H, dd, J_1 = 13.8 Hz, J_2 = 6.7 Hz), 2.91 (1H, dd, J_1 = 13.8 Hz, J_2 = 7.6 Hz), 2.45 (3H, s), 2.09 (3H, s).

$^{13}C\{^1H\}$ NMR (~101 MHz, $CDCl_3$): δ_C 171.2, 170.8, 158.7, 158.4, 136.6, 129.1, 128.6, 126.8, 101.3, 64.5, 49.4, 37.4, 20.7, 12.2.

HRMS (ESI): *m/z* $(M + Na)^+$ calcd for $C_{16}H_{18}N_2NaO_4$: 325.1164 found: 325.1175.

2-Benzamido-3-phenylpropyl acetate (3d-(RS)):



3d-(*RS*)

Compound **3d**-(RS) was obtained from procedures A and B after purification by column chromatography on silica gel (EtOAc:hexanes = 40:60) as a colourless solid (100 mg, 34%, 1 mmol scale). R_f (EtOAc/hexanes = 40:60) 0.5. mp: 138-140 ^oC.

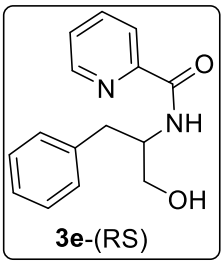
IR (DCM): 3308, 1733, 1535 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ_H 7.72-7.70 (2H, m), 7.51-7.47 (1H, m), 7.43-7.39 (2H, m), 7.33-7.29 (2H, m), 7.26-7.21 (3H, m), 6.51 (1H, d, J = 8.0 Hz), 4.64-4.59 (1H, m), 4.22 (1H, dd, J_1 = 11.5 Hz, J_2 = 6.0 Hz), 4.13 (1H, dd, J_1 = 11.5 Hz, J_2 = 4.2 Hz), 3.04 (1H, dd, J_1 = 13.7 Hz, J_2 = 6.0 Hz), 2.90 (1H, dd, J_1 = 13.8 Hz, J_2 = 7.9 Hz), 2.08 (3H, s).

$^{13}C\{^1H\}$ NMR (~101 MHz, $CDCl_3$): δ_C 171.5, 167.1, 137.0, 134.3, 131.6, 129.3, 128.7, 128.6, 126.9, 126.9, 64.8, 50.3, 37.5, 20.9.

HRMS (ESI): *m/z* $(M + Na)^+$ calcd for $C_{18}H_{19}NNaO_3$: 320.1263 found: 320.1270.

***N*-(1-Hydroxy-3-phenylpropan-2-yl)picolinamide (3e-(RS)):**



3e-(RS)

Compound **3e**-(RS) was obtained from procedure A after purification by column chromatography on silica gel (EtOAc:hexanes = 50:50) as a colourless solid (750 mg, 58%, 5 mmol scale); R_f(EtOAc/hexanes = 50:50) 0.3; mp: 98-100 ^oC;

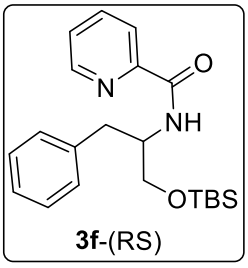
IR (DCM): 3372, 1659, 1523 cm^{-1};

^1H NMR (400 MHz, $CDCl_3$): δ_H 8.47 (1H, d, J = 4.2 Hz), 8.34 (1H, d, J = 8.0 Hz), 8.12 (1H, d, J = 7.8 Hz), 7.78 (1H, t, J = 7.7 Hz), 7.38-7.35 (1H, m), 7.27-7.26 (4H, m), 7.22-7.17 (1H, m), 4.39-4.35 (1H, m), 3.78 (1H, dd, J_1 = 11.1 Hz, J_2 = 3.7 Hz), 3.69 (1H, dd, J_1 = 11.1 Hz, J_2 = 5.1 Hz), 3.57 (1H, br. s), 3.05-2.95 (2H, m);

$^{13}C\ \{^1H\}$ NMR (~101 MHz, $CDCl_3$): δ_C 164.6, 149.5, 148.0, 137.7, 137.3, 129.2, 128.5, 126.5, 126.1, 122.2, 63.8, 53.0, 37.1.

HRMS (ESI): *m/z* $(M + Na)^+$ calcd for $C_{15}H_{16}N_2NaO_2$: 279.1109; found: 279.1118.

***N*-(1-((*Tert*-butyldimethylsilyl)oxy)-3-phenylpropan-2-yl)picolinamide (3f-(RS)):**



3f-(RS)

Compound **3f**-(RS) was obtained from procedure A and P after purification by column chromatography on silica gel (EtOAc:hexanes = 20:80) as a colourless liquid (200 mg, 81%, 0.67 mmol scale); R_f (EtOAc/hexanes = 20:80) 0.5;

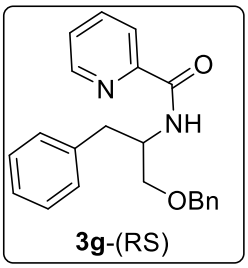
IR (DCM): 3380, 1677, 1517 cm^{-1};

^1H NMR (400 MHz, $CDCl_3$): δ_H 8.55 (1H, d, J = 4.7 Hz), 8.45 (1H, d, J = 8.9 Hz), 8.20 (1H, d, J = 7.8 Hz), 7.85 (1H, td, J_1 = 7.7 Hz, J_2 = 1.7 Hz), 7.44-7.41 (1H, m), 7.32-7.31 (4H, m), 7.25-7.22 (1H, m), 4.41-4.37 (1H, m), 3.68-3.61 (2H, m), 3.07-2.98 (2H, m), 0.98 (9H, s), 0.91 (3H, s), 0.80 (3H, s);

^{13}C {^1H} NMR (~101 MHz, $CDCl_3$): δ_C 163.7, 150.0, 148.1, 138.3, 137.2, 129.5, 128.4, 126.3, 126.0, 122.1, 62.6, 51.8, 37.2, 25.9, 18.3, -5.4, -5.5.

HRMS (ESI): *m/z* $(M + Na)^+$ calcd for $C_{21}H_{30}N_2NaO_2Si$: 393.1974; found: 393.1978.

***N*-(1-(Benzyloxy)-3-phenylpropan-2-yl)picolinamide (3g-(RS)):**



3g-(RS)

Compound **3g**-(RS) was obtained from procedure A and Q after purification by column chromatography on silica gel (EtOAc:hexanes = 20:80) as a colourless liquid (103 mg, 50%, 0.6 mmol scale); R_f (EtOAc/hexanes = 20:80) 0.4;

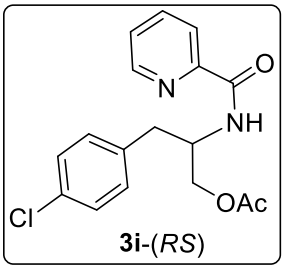
IR (DCM): 3353, 1676, 1518 cm^{-1};

^1H NMR (400 MHz, $CDCl_3$): δ_H 8.56-8.55 (1H, m), 8.40 (1H, d, J = 8.8 Hz), 8.17 (1H, d, J = 7.8 Hz), 7.82 (1H, td, J_1 = 7.7 Hz, J_2 = 1.7 Hz), 7.42-7.17 (11H, m), 4.57 (1H, d, J = 12.0 Hz), 4.51 (1H, d, J = 12.0 Hz), 4.52-4.48 (1H, m), 3.53-3.48 (2H, m), 3.03 (2H, d, J = 7.2 Hz).

^{13}C {^1H} NMR (~101 MHz, $CDCl_3$): δ_C 163.8, 149.9, 148.1, 138.1, 138.1, 137.3, 129.5, 128.4, 128.4, 127.8, 127.7, 126.4, 126.1, 122.2, 73.2, 69.7, 50.5, 37.6.

HRMS (ESI): *m/z* $(M + Na)^+$ calcd for $C_{22}H_{22}N_2NaO_2$: 369.1579; found: 369.1581.

3-(4-Chlorophenyl)-2-(picolinamido)propyl acetate (3i-(RS))



3i-(*RS*)

Compound **3i**-(RS) was obtained from procedures A and B after purification by column chromatography on silica gel (EtOAc:hexanes = 50:50) as a colourless solid (221 mg, 66%, 2 mmol scale). R_f (EtOAc/hexanes = 50:50) 0.5. mp: 86-88 ^{o}C.

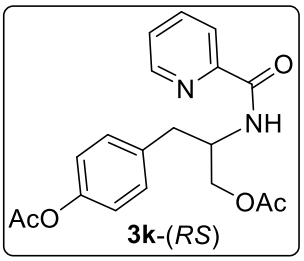
IR (DCM): 3373, 1743, 1523 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ_H 8.53 (1H, dd, J_1 = 4.7 Hz, J_2 = 0.6 Hz), 8.19 (1H, d, J = 8.9 Hz), 8.15 (1H, d, J = 7.8 Hz), 7.83 (1H, td, J_1 = 7.7 Hz, J_2 = 1.1 Hz), 7.44-7.41 (1H, m), 7.24 (2H, d, J = 8.4 Hz), 7.17 (2H, d, J = 8.4 Hz), 4.63-4.55 (1H, m), 4.14 (2H, d, J = 4.8 Hz), 2.98 (1H, dd, J_1 = 13.9 Hz, J_2 = 6.8 Hz), 2.91 (1H, dd, J_1 = 13.9 Hz, J_2 = 7.4 Hz), 2.09 (3H, s).

^{13}C{^{1}H} NMR (~101 MHz, $CDCl_3$): δ_C 170.9, 164.0, 149.4, 148.2, 137.4, 135.6, 132.6, 130.6, 128.7, 126.4, 122.3, 64.8, 49.4, 37.1, 20.9.

HRMS (ESI): *m/z* (M + H)$^{+}$ calcd for $C_{17}H_{18}ClN_2O_3$: 333.1006; found: 333.1013.

4-(3-Acetoxy-2-(picolinamido)propyl)phenyl acetate (3k-(RS))



3k-(*RS*)

Compound **3k**-(RS) was obtained from procedures R, S, T and U after purification by column chromatography on silica gel (EtOAc:hexanes = 50:50) as a colourless solid (690 mg, 65%, 3 mmol scale). R_f (EtOAc/hexanes = 50:50) 0.5. mp: 108-110 ^{o}C.

IR (DCM): 3366, 1739, 1511 cm^{-1}.

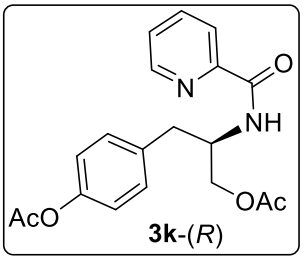
^{1}H NMR (400 MHz, $CDCl_3$): δ_H 8.55 (1H, d, J = 4.7 Hz), 8.23 (1H, d, J = 8.9 Hz), 8.17 (1H, d, J = 7.8 Hz), 7.84 (1H, td, J_1 = 7.7 Hz, J_2 = 1.4 Hz), 7.45-7.42 (1H, m), 7.26 (2H, d, J = 9.4 Hz), 7.02 (2H, d, J = 8.4 Hz), 4.65-4.59 (1H, m), 4.18 (2H, d, J = 4.8 Hz), 3.03 (1H, dd, J_1 = 13.9 Hz, J_2 = 6.5 Hz), 2.95 (1H**,** dd, J_1 = 13.9 Hz, J_2 = 7.6 Hz), 2.27 (3H, s), 2.10 (3H, s).

^{13}C{^{1}H} NMR (~101 MHz, $CDCl_3$): δ_C 170.9, 169.5, 164.0, 149.5, 149.4, 148.1, 137.4, 134.7, 130.2, 126.3, 122.3, 121.7, 64.7, 49.4, 37.1, 21.1, 20.9.

HRMS (ESI): *m/z* (M + Na)$^{+}$ calcd for $C_{19}H_{20}N_2NaO_5$: 379.1270; found: 379.1261.

The HPLC of compound **3k**-(RS) was determined by using the Daicel Chiralpak IA column, hexane/*i*-PrOH 50:50, flow rate 1.0 mL/min, UV detection at 254 nm, t_R = 7.94 min, t_S = 7.29 min.

(R)-4-(3-Acetoxy-2-(picolinamido)propyl)phenyl acetate (3k-(R)):



3k-(*R*)

Compound **3k**-(R) was obtained from procedures R, S, T and U after purification by column chromatography on silica gel (EtOAc:hexanes = 50:50) as a colourless solid (670 mg, 63%, 3 mmol scale). R_f (EtOAc/hexanes = 50:50) 0.5. mp: 110-112 ºC.

IR (DCM): 3363, 1739, 1511 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ_H 8.55 (1H, d, J = 4.6 Hz), 8.22 (1H, d, J = 8.9 Hz), 8.17 (1H, d, J = 7.8 Hz), 7.85 (1H, td, J_1 = 7.7 Hz, J_2 = 1.6 Hz), 7.45-7.42 (1H, m), 7.26 (2H, d, J = 8.2 Hz), 7.02 (2H, d, J = 8.4 Hz), 4.65-4.59 (1H, m), 4.18 (2H, d, J = 4.8 Hz), 3.03 (1H, dd, J_1 = 13.9 Hz, J_2 = 6.5 Hz), 2.95 (1H, dd, J_1 = 13.9 Hz, J_2 = 7.7 Hz), 2.28 (3H, s), 2.10 (3H, s).

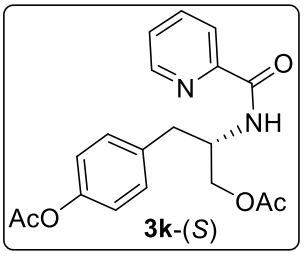
$^{13}C\{^1H\}$ NMR (~101 MHz, $CDCl_3$): δ_C 170.8, 169.4, 163.9, 149.4, 149.3, 148.1, 137.3, 134.6, 130.1, 126.2, 122.2, 121.6, 64.6, 49.3, 37.0, 21.0, 20.8;

HRMS (ESI): *m/z* $(M + H)^+$ calcd for $C_{19}H_{21}N_2O_5$: 357.1450; found: 357.1440.

$(\alpha)^{25}_D$ = 49.9 (c = 0.03 g/mL, $CHCl_3$).

The enantiomeric ratio (*er* 98:2) of compound **3k**-(R) was determined by using the Daicel Chiralpak IA column, hexane/*i*-PrOH 50:50, flow rate 1.0 mL/min, UV detection at 254 nm, t_R = 7.91 min, t_S = 7.29 min.

(S)-4-(3-Acetoxy-2-(picolinamido)propyl)phenyl acetate (3k-(S)):



3k-(*S*)

Compound **3k**-(S) was obtained from procedures R, S, T and U after purification by column chromatography on silica gel (EtOAc:hexanes = 50:50) as a colourless solid (675 mg, 63%, 3 mmol scale). R_f (EtOAc/hexanes = 50:50) 0.5. mp: 108-110 ºC.

IR (DCM): 3379, 1739, 1511 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ_H 8.56 (1H, d, J = 4.4 Hz), 8.28 (1H, d, J = 8.1 Hz), 8.19 (1H, d, J = 7.7 Hz), 7.87 (1H, t, J = 7.6 Hz), 7.46 (1H, t, J = 6.2 Hz), 7.26 (2H, d, J = 8.4 Hz), 7.02 (2H, d, J = 8.4 Hz), 4.65-4.59 (1H, m), 4.18 (2H, d, J = 4.8 Hz), 3.03 (1H, dd, J_1 = 13.9 Hz, J_2 = 6.6 Hz), 2.95 (1H, dd, J_1 = 13.9 Hz, J_2 = 7.6 Hz), 2.28 (3H, s), 2.10 (3H, s).

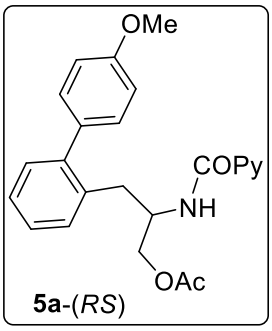
$^{13}C\{^1H\}$ NMR (~101 MHz, $CDCl_3$): δ_C 170.9, 169.5, 163.8, 149.4, 149.3, 147.9, 137.7, 134.7, 130.2, 126.4, 122.5, 121.7, 64.7, 49.5, 37.1, 21.1, 20.9.

HRMS (ESI): *m/z* $(M + Na)^+$ calcd for $C_{19}H_{20}N_2NaO_5$: 379.1270; found: 379.1261.

$(\alpha)^{25}_D$ = -43.3 (c = 0.03 g/mL, $CHCl_3$).

The enantiomeric ratio (*er* 98:2) of compound **3k**-(S) was determined by using the Daicel Chiralpak IA column, hexane/*i*-PrOH 50:50, flow rate 1.0 mL/min, UV detection at 254 nm, t_R = 8.11 min, t_S = 7.44 min.

3-(4'-Methoxy-(1,1'-biphenyl)-2-yl)-2-(picolinamido)propyl acetate (5a-(RS)):



Compound **5a**-(RS) was obtained from procedure C after purification by column chromatography on silica gel (EtOAc:hexanes = 40:60) as a yellow coloured semi-solid (9 mg, 11%, 0.20 mmol scale).

R_f (EtOAc/hexanes = 40:60) 0.4.

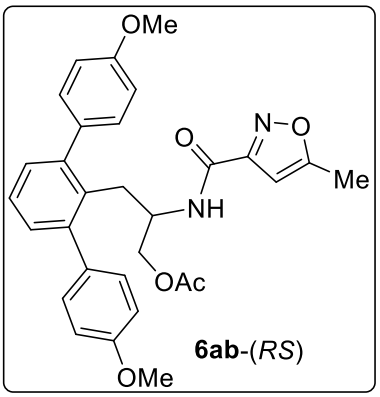
IR (DCM): 3366, 1742, 1519 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ_H 8.57-8.55 (1H, m), 8.15 (1H, d, J = 7.8 Hz), 8.05 (1H, d, J = 9.0 Hz), 7.84 (1H, td, J_1 = 7.7 Hz, J_2 = 1.7 Hz), 7.46-7.42 (2H, m), 7.31-7.19 (5H, m), 6.97 (2H, dt, J_1 = 8.7 Hz, J_2 = 2.9 Hz), 4.53-4.47 (1H, m), 3.99-3.92 (2H, m), 3.88 (3H, s), 3.12 (1H, dd, J_1 = 13.9 Hz, J_2 = 7.6 Hz), 2.96 (1H, dd, J_1 = 13.9 Hz, J_2 = 7.2 Hz), 1.92 (3H, s).

$^{13}C\{^1H\}$ NMR (~101 MHz, $CDCl_3$): δ_C 170.8, 163.8, 158.6, 149.6, 148.0, 142.2, 137.3, 135.0, 133.8, 130.5, 130.5, 129.9, 127.4, 126.6, 126.2, 122.3, 113.6, 64.9, 55.3, 49.8, 34.3, 20.7.

HRMS (ESI): *m/z* $(M + H)^+$ calcd for $C_{24}H_{25}N_2O_4$: 405.1814 found: 405.1825.

3-(4,4''-Dimethoxy-(1,1':3',1''-terphenyl)-2'-yl)-2-(5-methylisoxazole-3-carboxamido)propyl acetate (6ab-(RS)):



Compound **6ab**-(RS) was obtained from procedure C after purification by column chromatography on silica gel (EtOAc:hexanes = 40:60) as a yellow coloured solid (54 mg, 52%, 0.20 mmol scale). R_f (EtOAc/hexanes = 40:60) 0.3. mp: 165-167 ^oC.

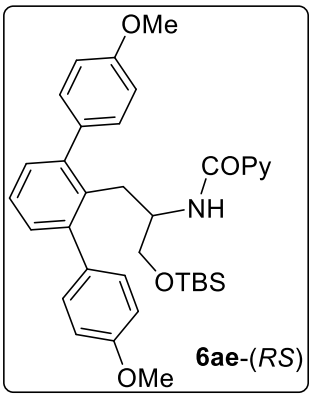
IR (DCM): 3423, 1738, 1518 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ_H 7.29-7.28 (4H, dt, J_1 = 8.7 Hz, J_2 = 2.9 Hz), 7.25-7.22 (1H, m), 7.14 (2H, d, J = 7.1 Hz), 7.00-6.96 (4H, dt, J_1 = 8.7 Hz, J_2 = 2.9 Hz), 6.28 (1H, s), 6.22 (1H, d, J = 9.2 Hz), 4.06-4.00 (1H, m), 3.87 (6H, s), 3.68-3.61 (2H, m), 3.08-2.97 (2H, m), 2.44 (3H, s), 1.78 (3H, s).

$^{13}C\{^1H\}$ NMR (~101 MHz, $CDCl_3$): δ_C 170.9, 170.6, 158.7, 158.4, 158.3, 143.2, 134.3, 132.7, 130.6, 129.7, 126.3, 113.8, 101.3, 65.3, 55.3, 48.4, 30.8, 20.6, 12.3.

HRMS (ESI): *m/z* $(M + H)^+$ calcd for $C_{30}H_{31}N_2O_6$: 515.2182 found: 515.2184.

***N*-(1-((*Tert*-butyldimethylsilyl)oxy)-3-(4,4''-dimethoxy-(1,1':3',1''-terphenyl)-2'-yl)propan-2-yl)picolinamide (6ae-(RS)):**



Compound **6ae**-(RS) was obtained from procedure C after purification by column chromatography on silica gel (EtOAc:hexanes = 20:80) as a colourless liquid (29 mg, 50%, 0.1 mmol scale); R_f (EtOAc/hexanes = 20:80) 0.3;

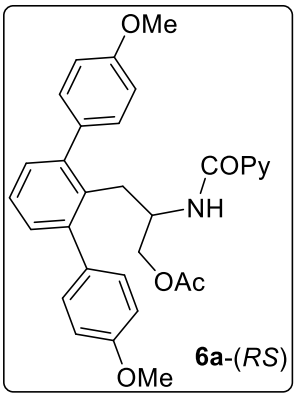
IR (DCM): 3377, 1678, 1515 cm^{-1};

^1H NMR (400 MHz, $CDCl_3$): δ_H 8.55 (1H, d, J = 4.6 Hz), 8.03 (1H, d, J = 7.8 Hz), 7.79 (1H, td, J_1 = 7.7 Hz, J_2 = 1.7 Hz), 7.66 (1H, d, J = 9.7 Hz), 7.42-7.39 (1H, m), 7.32 (4H, d, J = 8.5 Hz), 7.20-7.17 (1H, m), 7.10 (2H, d, J = 7.1 Hz), 6.97 (4H, d, J = 8.7 Hz), 3.98-3.91 (1H, m), 3.89 (6H, s), 3.30 (1H, dd, J_1 = 10.0 Hz, J_2 = 4.2 Hz), 3.25-3.19 (2H, m), 3.04 (1H, dd, J_1 = 14.1 Hz, J_2 = 3.6 Hz), 0.74 (9H, s), -0.14 (3H, s), -0.19 (3H, s);

^{13}C {^1H} NMR (~101 MHz, $CDCl_3$): δ_C 163.4, 158.4, 150.0, 147.6, 143.2, 137.0, 134.8, 134.1, 130.8, 129.5, 125.8, 125.7, 122.0, 113.5, 65.4, 55.2, 50.8, 31.2, 25.7, 18.0, -5.5, -5.8.

HRMS (ESI): *m/z* $(M + H)^+$ calcd for $C_{35}H_{43}N_2O_4Si$: 583.2992; found: 583.2994.

3-(4,4''-Dimethoxy-(1,1':3',1''-terphenyl)-2'-yl)-2-(picolinamido)propyl acetate (6a-(RS)):



Compound **6a**-(RS) was obtained from procedure C after purification by column chromatography on silica gel (EtOAc:hexanes = 40:60) as a yellow coloured solid (71 mg, 70%, 0.20 mmol scale). R_f (EtOAc/hexanes = 40:60) 0.3. mp: 126-128 ºC.

IR (DCM): 3375, 1741, 1515 cm^{-1}.

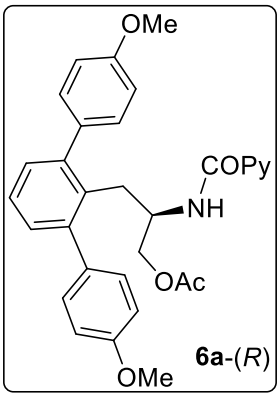
^1H NMR (400 MHz, $CDCl_3$): δ_H 8.53 (1H, d, J = 4.6 Hz), 8.01 (1H, d, J = 7.8 Hz), 7.78 (1H, td, J_1 = 7.7 Hz, J_2 = 1.6 Hz), 7.47 (1H, d, J = 9.2 Hz), 7.41-7.38 (1H,m), 7.30 (4H, d, J = 8.6 Hz), 7.22-7.18 (1H, m), 7.10 (2H, d, J = 7.6 Hz), 6.97 (4H, d, J = 8.6 Hz), 4.13-4.04 (1H, m), 3.87 (6H, s), 3.71 (1H, dd, J_1 = 11.0 Hz, J_2 = 4.5 Hz), 3.66 (1H, dd, J_1 = 11.0 Hz, J_2 = 5.1 Hz), 3.12 (1H, dd, J_1 = 14.1 Hz, J_2 = 5.1 Hz), 3.05 (1H, dd, J_1 = 14.0 Hz, J_2 = 9.7 Hz), 1.80 (3H, s).

^{13}C{^1H} NMR (~101 MHz, $CDCl_3$): δ_C 170.6, 163.4, 158.5, 149.5, 147.6, 143.1, 137.1, 134.3, 133.0, 130.7, 129.6, 126.1, 126.0, 122.1, 113.6, 65.5, 55.2, 48.5, 31.0, 20.5.

HRMS (ESI): *m/z* $(M + H)^+$ calcd for $C_{31}H_{31}N_2O_5$: 511.2233 found: 511.2251.

The HPLC of compound **6a**-(RS) was determined by using the Daicel Chiralpak IC column, hexane/*i*-PrOH 40:60, flow rate 1.0 mL/min, UV detection at 254 nm, t_R = 9.83 min, t_S = 12.03 min.

(R)-3-(4,4''-Dimethoxy-(1,1':3',1''-terphenyl)-2'-yl)-2-(picolinamido)propyl acetate (6a-(R)):



Compound **6a**-(R) was obtained from procedure C after purification by column chromatography on silica gel (EtOAc:hexanes = 40:60) as a yellow coloured solid (94 mg, 74%, 0.25 mmol scale). R_f (EtOAc/hexanes = 40:60) 0.3. mp: 124-126 ºC.

IR (DCM): 3375, 1740, 1514 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ_H 8.53 (1H, d, J = 4.7 Hz), 8.01 (1H, d, J = 7.8 Hz), 7.78 (1H, td, J_1 = 7.7 Hz, J_2 = 1.6 Hz), 7.47 (1H, d, J = 9.2 Hz), 7.41-7.38 (1H, m), 7.30 (4H, d, J = 8.6 Hz), 7.22-7.18 (1H, m), 7.11 (2H, d, J = 7.7 Hz), 6.97 (4H, d, J = 8.6 Hz), 4.14-4.04 (1H, m), 3.86 (6H, s), 3.71 (1H, dd, J_1 = 11.0 Hz, J_2 = 4.5 Hz), 3.65 (1H, dd, J_1 = 11.0 Hz, J_2 = 5.1 Hz), 3.12 (1H, dd, J_1 = 14.1 Hz, J_2 = 5.1 Hz), 3.05 (1H, dd, J_1 = 14.0 Hz, J_2 = 9.7 Hz), 1.80 (3H, s).

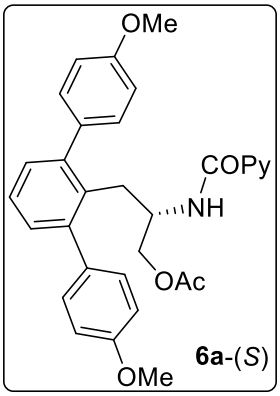
$^{13}C\{^1H\}$ NMR (~101 MHz, $CDCl_3$): δ_C 170.6, 163.4, 158.5, 149.5, 147.6, 143.1, 137.1, 134.3, 133.1, 130.7, 129.6, 126.1, 126.0, 122.1, 113.6, 65.5, 55.2, 48.5, 31.0, 20.6.

HRMS (ESI): *m/z* $(M + H)^+$ calcd for $C_{31}H_{31}N_2O_5$: 511.2233 found: 511.2242.

$(\alpha)^{25}_D$ = 55.2 (c = 0.03 g/mL, $CHCl_3$).

The enantiomeric ratio (*er* 96:4) of compound **6a**-(R) was determined by using the Daicel Chiralpak IC column, hexane/*i*-PrOH 40:60, flow rate 1.0 mL/min, UV detection at 254 nm, t_R = 9.91 min, t_S = 12.27 min.

(S)-3-(4,4''-Dimethoxy-(1,1':3',1''-terphenyl)-2'-yl)-2-(picolinamido)propyl acetate (6a-(S)):



Compound **6a**-(S) was obtained from procedure C after purification by column chromatography on silica gel (EtOAc:hexanes = 40:60) as a yellow coloured solid (87 mg, 68%, 0.25 mmol scale). R_f (EtOAc/hexanes = 40:60) 0.3. mp: 124-126 ºC.

IR (DCM): 3374, 1741, 1515 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ_H 8.53 (1H, d, J = 4.3 Hz), 8.01 (1H, d, J = 7.8 Hz), 7.77 (1H, td, J_1 = 7.7 Hz, J_2 = 1.6 Hz), 7.48 (1H, d, J = 9.2 Hz), 7.40-7.37 (1H, m), 7.30 (4H, d, J = 8.6 Hz), 7.22-7.18 (1H,

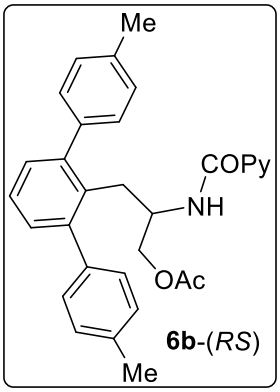
m), 7.11 (2H, d, J = 7.5 Hz), 6.97 (4H, d, J = 8.6 Hz), 4.14-4.04 (1H, m), 3.86 (6H, s), 3.72 (1H, dd, J_1 = 11.0 Hz, J_2 = 4.5 Hz), 3.66 (1H, dd, J_1 = 11.0 Hz, J_2 = 5.1 Hz), 3.12 (1H, dd, J_1 = 14.0 Hz, J_2 = 5.1 Hz), 3.05 (1H, dd, J_1 = 14.0 Hz, J_2 = 9.7 Hz), 1.79 (3H, s).

$^{13}C\{^1H\}$ NMR (~126 MHz, $CDCl_3$): δ_C 170.5, 163.4, 158.6, 149.6, 147.6, 143.1, 137.1, 134.4, 133.1, 130.7, 129.6, 126.1, 125.9, 122.1, 113.6, 65.6, 55.2, 48.6, 31.1, 20.5.

HRMS (ESI): m/z $(M + H)^+$ calcd for $C_{31}H_{31}N_2O_5$: 511.2233 found: 511.2251.

$(\alpha)^{25}_D$ = -59.9 (c = 0.03 g/mL, $CHCl_3$). The enantiomeric ratio (*er* 96:4) of compound **6a**-(S) was determined by using the Daicel Chiralpak IC column, hexane/*i*-PrOH 40:60, flow rate 1.0 mL/min, UV detection at 254 nm, t_R = 9.69 min, t_S = 11.89 min.

3-(4,4''-Dimethyl-(1,1':3',1''-terphenyl)-2'-yl)-2-(picolinamido)propyl acetate (6b-(RS)):



Compound **6b**-(RS) was obtained from procedure C (t-amylOH is used) after purification by column chromatography on silica gel (EtOAc:hexanes = 40:60) as a colourless solid (64 mg, 67%, 0.20 mmol scale). R_f (EtOAc/hexanes = 40:60) 0.6. mp: 88-90 ^oC.

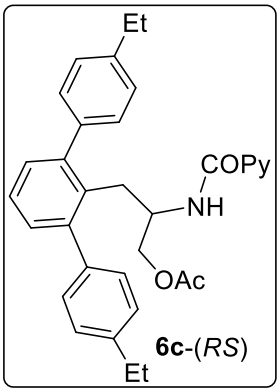
IR (DCM): 3375, 1739, 1513 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ_H 8.53 (1H, dd, J_1 = 4.7 Hz, J_2 = 0.7 Hz), 8.01 (1H, d, J = 7.8 Hz), 7.76 (1H, td, J_1 = 7.7 Hz, J_2 = 1.7 Hz), 7.46 (1H, d, J = 9.2 Hz), 7.40-7.37 (1H, m), 7.27 (4H, d, J = 8.1 Hz), 7.23 (4H, d, J = 8.1 Hz), 7.22-7.19 (1H, m), 7.12 (2H, d, J = 7.1 Hz), 4.11-4.04 (1H, m), 3.70 (1H, dd, J_1 = 11.0 Hz, J_2 = 4.5 Hz), 3.64 (1H, dd, J_1 = 11.0 Hz, J_2 = 5.1 Hz), 3.13 (1H, dd, J_1 = 14.0 Hz, J_2 = 5.1 Hz), 3.04 (1H, dd, J_1 = 14.0 Hz, J_2 = 9.7 Hz), 2.41 (6H, s), 1.77 (3H, s).

$^{13}C\{^1H\}$ NMR (~101 MHz, $CDCl_3$): δ_C 170.6, 163.4, 149.6, 147.6, 143.4, 139.0, 137.1, 136.5, 132.7, 129.5, 129.5, 128.9, 126.1, 125.9, 122.1, 65.5, 48.6, 31.0, 21.2, 20.5.

HRMS (ESI): m/z $(M + H)^+$ calcd for $C_{31}H_{31}N_2O_3$: 479.2335 found: 479.2354.

3-(4,4''-Diethyl-(1,1':3',1''-terphenyl)-2'-yl)-2-(picolinamido)propyl acetate (6c-(RS)):



Compound **6c**-(RS) was obtained from procedure C after purification by column chromatography on silica gel (EtOAc:hexanes = 40:60) as a yellow coloured semi solid (53 mg, 52%, 0.20 mmol scale). R_f (EtOAc/hexanes = 40:60) 0.6.

IR (DCM): 3380, 1742, 1515 cm^{-1}.

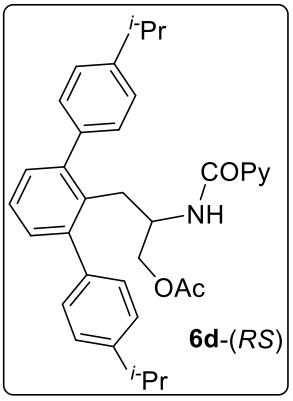
^1H NMR (400 MHz, $CDCl_3$): δ_H 8.53 (1H, d, J = 4.6 Hz), 8.01 (1H, d, J = 7.8 Hz), 7.78 (1H, td, J_1 = 7.7 Hz, J_2 = 1.6 Hz), 7.47 (1H, d, J = 9.2 Hz), 7.41-7.38 (1H, m), 7.30 (4H, d, J = 8.0 Hz), 7.27 (4H, d, J =

8.0 Hz), 7.23-7.19 (1H, m), 7.13 (2H, d, J = 7.4 Hz), 4.10-4.04 (1H, m), 3.71-3.62 (2H, m), 3.13 (1H, dd, J_1 = 14.0 Hz, J_2 = 5.1 Hz), 3.04 (1H, dd, J_1 = 14.0 Hz, J_2 = 9.8 Hz), 2.72 (4H, q, J = 7.6 Hz), 1.76 (3H, s), 1.30 (6H, t, J = 7.6 Hz).

$^{13}C\{^1H\}$ NMR (~101 MHz, $CDCl_3$): δ_C 170.6, 163.5, 149.7, 147.7, 143.5, 142.9, 139.3, 137.2, 132.8, 129.6, 127.8, 126.1, 126.0, 122.2, 65.6, 48.6, 31.1, 28.6, 20.6, 15.5.

HRMS (ESI): *m/z* $(M + H)^+$ calcd for $C_{33}H_{35}N_2O_3$: 507.2648 found: 507.2662.

3-(4,4''-Diisopropyl-(1,1':3',1''-terphenyl)-2'-yl)-2-(picolinamido)propyl acetate (6d-(RS)):



Compound **6d**-(RS) was obtained from procedure C after purification by column chromatography on silica gel (EtOAc:hexanes = 40:60) as a yellow coloured semi-solid (70 mg, 53%, 0.25 mmol scale). R_f (EtOAc/hexanes = 40:60) 0.65.

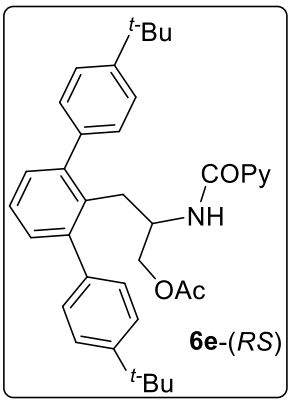
IR (DCM): 3376, 1740, 1514 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ_H 8.53 (1H, d, J = 4.1 Hz), 8.01 (1H, d, J = 7.8 Hz), 7.78 (1H, td, J_1 = 7.7 Hz, J_2 = 1.6 Hz), 7.48 (1H, d, J = 9.2 Hz), 7.41-7.38 (1H, m), 7.31 (4H, d, J = 8.44 Hz), 7.30 (4H, d, J = 8.44 Hz), 7.23-7.19 (1H, m), 7.15-7.13 (2H, m), 4.11-4.03 (1H, m), 3.66-3.65 (2H, m), 3.13 (1H, dd, J_1 = 14.0 Hz, J_2 = 5.3 Hz), 3.07-2.94 (3H, m), 1.75 (3H, s), 1.31 (12H, d, J = 6.9 Hz).

$^{13}C\{^1H\}$ NMR (~101 MHz, $CDCl_3$): δ_C 170.6, 163.4, 149.7, 147.7, 147.5, 143.5, 139.4, 137.2, 132.8, 129.6, 126.3, 126.1, 126.0, 122.2, 65.5, 48.5, 33.8, 31.1, 24.1, 24.0, 20.7.

HRMS (ESI): *m/z* $(M + H)^+$ calcd for $C_{35}H_{39}N_2O_3$: 535.2961 found: 535.2959.

3-(4,4''-Di-*tert*-butyl-(1,1':3',1''-terphenyl)-2'-yl)-2-(picolinamido)propyl acetate (6e-(RS)):



Compound **6e**-(RS) was obtained from procedure C after purification by column chromatography on silica gel (EtOAc:hexanes = 40:60) as a yellow coloured semi-solid (90 mg, 64%, 0.25 mmol scale). R_f (EtOAc/hexanes = 40:60) 0.7.

IR (DCM): 3384, 1741, 1514 cm^{-1}.

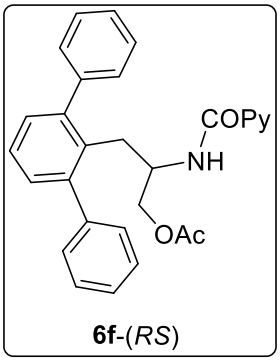
^1H NMR (400 MHz, $CDCl_3$): δ_H 8.52 (1H, d, J = 4.5 Hz), 8.00 (1H, d, J = 7.8 Hz), 7.75 (1H, td, J_1 = 7.7 Hz, J_2 = 1.4 Hz), 7.50 (1H, d, J = 9.3 Hz), 7.45 (4H, d, J = 8.2 Hz), 7.39-7.36 (1H, m), 7.32 (4H, d, J = 8.2 Hz), 7.23-7.19 (1H, m), 7.14 (2H, d, J = 6.8 Hz), 4.13-4.04 (1H, m), 3.69-3.62 (2H, m),

3.16 (1H, dd, J_1 = 14.0 Hz, J_2 = 5.3 Hz), 3.05 (1H, dd, J_1 = 13.9 Hz, J_2 = 9.5 Hz), 1.74 (3H, s), 1.38 (18H, s).

$^{13}C\{^1H\}$ NMR (~101 MHz, $CDCl_3$): δ_C 170.5, 163.3, 149.6, 147.6, 143.4, 139.0, 137.1, 132.8, 129.5, 129.2, 126.1, 125.9, 125.1, 122.1, 65.4, 48.4, 34.5, 31.4, 31.0, 20.6.

HRMS (ESI): *m/z* $(M + H)^+$ calcd for $C_{37}H_{43}N_2O_3$: 563.3274 found: 563.3290.

3-((1,1':3',1''-Terphenyl)-2'-yl)-2-(picolinamido)propyl acetate (6f-(RS)):



6f-(*RS*)

Compound **6f**-(RS) was obtained from procedure C after purification by column chromatography on silica gel (EtOAc:hexanes = 40:60) as a yellow coloured semi-solid (61 mg, 68%, 0.20 mmol scale). R_f (EtOAc/hexanes = 40:60) 0.6.

IR (DCM): 3372, 1741, 1516 cm^{-1}.

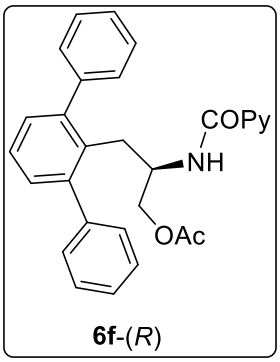
^1H NMR (400 MHz, $CDCl_3$): δ_H 8.52 (1H, d, J = 4.7 Hz), 8.02 (1H, d, J = 7.8 Hz), 7.77 (1H, td, J_1 = 7.7 Hz, J_2 = 1.7 Hz), 7.51-7.36 (12H, m), 7.26-7.22 (1H, m), 7.16-7.14 (2H, m), 4.12-4.04 (1H, m), 3.68-3.61 (2H, m), 3.12 (1H, dd, J_1 = 14.1 Hz, J_2 = 5.4 Hz), 3.05 (1H, dd, J_1 = 14.1 Hz, J_2 = 9.6 Hz), 1.76 (3H, s).

$^{13}C\{^1H\}$ NMR (~101 MHz, $CDCl_3$): δ_C 170.6, 163.4, 149.5, 147.6, 143.5, 141.9, 137.1, 132.5, 129.6, 128.2, 127.0, 126.1, 126.0, 122.1, 65.4, 48.4, 31.1, 20.6.

HRMS (ESI): *m/z* $(M + H)^+$ calcd for $C_{29}H_{27}N_2O_3$: 451.2022 found: 451.2023.

The HPLC of compound **6f**-(RS) was determined by using the Daicel Chiralpak IC column, hexane/*i*-PrOH 60:40, flow rate 1.0 mL/min, UV detection at 254 nm, t_R = 8.58 min, t_S = 11.25 min.

(R)-3-((1,1':3',1''-Terphenyl)-2'-yl)-2-(picolinamido)propyl acetate (6f-(R)):



6f-(*R*)

Compound **6f**-(R) was obtained from procedure C after purification by column chromatography on silica gel (EtOAc:hexanes = 40:60) as a yellow coloured semi-solid (72 mg, 64%, 0.25 mmol scale). R_f (EtOAc/hexanes = 40:60) 0.6.

IR (DCM): 3384, 1742, 1514 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ_H 8.52 (1H, d, J = 4.4 Hz), 8.02 (1H, d, J = 7.8 Hz), 7.77 (1H, t, J = 7.4 Hz), 7.49-7.38 (12H, m), 7.26-7.22 (1H, m), 7.15 (2H, d, J = 7.4 Hz), 4.12-4.04 (1H, m), 3.68-3.61 (2H, m), 3.12 (1H, dd, J_1 = 14.1 Hz, J_2 = 5.3 Hz), 3.04 (1H, dd, J_1 = 14.1 Hz, J_2 = 9.7 Hz), 1.76 (3H, s).

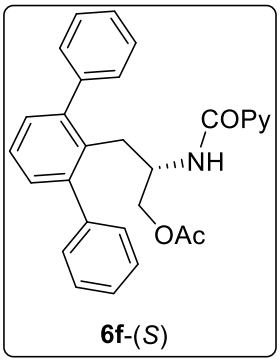
$^{13}C\{^{1}H\}$ NMR (~101 MHz, $CDCl_3$): δ_C 170.6, 163.4, 149.5, 147.7, 143.5, 141.9, 137.1, 132.5, 129.6, 128.2, 127.0, 126.2, 126.0, 122.1, 65.5, 48.4, 31.1, 20.6.

HRMS (ESI): *m/z* $(M + H)^+$ calcd for $C_{29}H_{27}N_2O_3$: 451.2022 found: 451.2036.

$(\alpha)^{25}_D$ = 60.1 (*c* = 0.02 g/mL, $CHCl_3$).

The enantiomeric ratio (*er* 98:2) of compound **6f**-(R) was determined by using the Daicel Chiralpak IC column, hexane/*i*-PrOH 60:40, flow rate 1.0 mL/min, UV detection at 254 nm, t_R = 8.47 min, t_S = 11.20 min.

(S)-3-((1,1':3',1''-Terphenyl)-2'-yl)-2-(picolinamido)propyl acetate (6f-(S)):



Compound **6f**-(S) was obtained from procedure C after purification by column chromatography on silica gel (EtOAc:hexanes = 40:60) as a yellow coloured semi-solid (67, 60 mg, %, 0.20 mmol scale). R_f (EtOAc/hexanes = 40:60) 0.6.

IR (DCM): 3370, 1742, 1515 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ_H 8.52 (1H, d, *J* = 4.3 Hz), 8.02 (1H, d, *J* = 7.8 Hz), 7.77 (1H, td, J_1 = 7.7 Hz, J_2 = 1.6 Hz), 7.49-7.36 (12H, m), 7.26-7.22 (1H, m), 7.15 (2H, d, *J* = 7.3 Hz), 4.12-4.04 (1H, m), 3.68-3.61 (2H, m), 3.11 (1H, dd, J_1 = 14.1 Hz, J_2 = 5.4 Hz), 3.04 (1H, dd, J_1 = 14.1 Hz, J_2 = 9.6 Hz), 1.76 (3H, s).

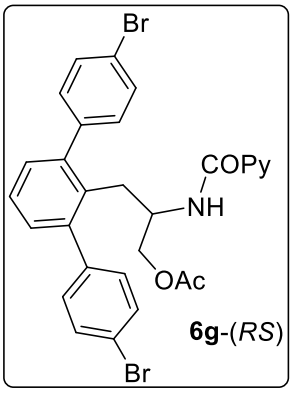
$^{13}C\{^{1}H\}$ NMR (~101 MHz, $CDCl_3$): δ_C 170.7, 163.5, 149.6, 147.7, 143.5, 142.0, 137.2, 132.6, 129.7, 128.3, 127.0, 126.2, 126.1, 122.2, 65.5, 48.5, 31.2, 20.7.

HRMS (ESI): *m/z* $(M + H)^+$ calcd for $C_{29}H_{27}N_2O_3$: 451.2022 found: 451.2025.

$(\alpha)^{25}_D$ = -64.1 (*c* = 0.02 g/mL, $CHCl_3$).

The enantiomeric ratio (*er* 98:2) of compound **6f**-(S) was determined by using the Daicel Chiralpak IC column, hexane/*i*-PrOH 60:40, flow rate 1.0 mL/min, UV detection at 254 nm, t_R = 8.74 min, t_S = 11.19 min.

3-(4,4''-Dibromo-(1,1':3',1''-terphenyl)-2'-yl)-2-(picolinamido)propyl acetate (6g-(RS)):



Compound **6g**-(RS) was obtained from procedure C after purification by column chromatography on silica gel (EtOAc:hexanes = 40:60) as a colourless solid (83 mg, 68%, 0.20 mmol scale). R_f(EtOAc/hexanes = 40:60) 0.6. mp: 130-132 °C.

IR (DCM): 3389, 1739, 1514 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ_H 8.55 (1H, d, *J* = 4.3 Hz), 8.00 (1H, d, *J* = 7.8 Hz), 7.80 (1H, td, J_1 = 7.7 Hz, J_2 = 1.6 Hz), 7.55 (4H, d, *J* = 8.3 Hz), 7.47-7.41 (2H, m), 7.26-7.21 (5H, m), 7.11 (2H, d, *J* = 7.5

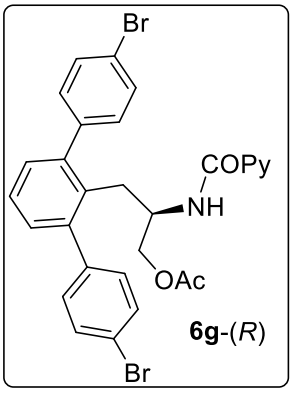
Hz), 4.12-4.06 (1H, m), 3.73 (1H, dd, J_1 = 11.0 Hz, J_2 = 4.4 Hz), 3.65 (1H, dd, J_1 = 11.1 Hz, J_2 = 5.4 Hz), 3.06 (1H, dd, J_1 = 14.1 Hz, J_2 = 4.7 Hz), 2.97 (1H, dd, J_1 = 14.1 Hz, J_2 = 10.0 Hz), 1.83 (3H, s).

$^{13}C\{^1H\}$ NMR (~101 MHz, $CDCl_3$): δ_C 170.5, 163.3, 149.2, 147.7, 142.3, 140.6, 137.2, 132.4, 131.4, 131.3, 129.7, 126.4, 126.2, 122.1, 121.3, 65.4, 48.6, 31.0, 20.6.

HRMS (ESI): *m/z* $(M + H)^+$ calcd for $C_{29}H_{25}Br_2N_2O_3$: 607.0232 found: 607.0237.

The HPLC of compound **6g**-(RS) was determined by using the Daicel Chiralpak IC column, hexane/*i*-PrOH 50:50, flow rate 1.0 mL/min, UV detection at 254 nm, t_R = 10.10 min, t_S = 13.96 min.

(R)-3-(4,4''-Dibromo-(1,1':3',1''-terphenyl)-2'-yl)-2-(picolinamido)propyl acetate (6g-(R)):



Compound **6g**-(R) was obtained from procedure C after purification by column chromatography on silica gel (EtOAc:hexanes = 40:60) as a colourless solid (104 mg, 68%, 0.25 mmol scale). R_f (EtOAc/hexanes = 40:60) 0.6. mp: 130-132 ^oC.

IR (DCM): 3389, 1739, 1513 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ_H 8.55 (1H, dd, J_1 = 4.7 Hz, $J_{2=}$ 0.6 Hz), 8.01 (1H, d, J = 7.8 Hz), 7.80 (1H, td, J_1 = 7.7 Hz, J_2 = 1.7 Hz), 7.55 (4H, d, J = 8.4 Hz), 7.46-7.41 (2H, m), 7.26-7.23 (5H, m), 7.11 (2H, d, J = 7.5 Hz), 4.12-4.05 (1H, m), 3.72 (1H, dd, J_1 = 11.0 Hz, J_2 = 4.4 Hz), 3.65 (1H, dd, J_1 = 11.1 Hz, J_2 = 5.4 Hz), 3.06 (1H, dd, J_1 = 14.1 Hz, J_2 = 4.7 Hz), 2.97 (1H, dd, J_1 = 14.1 Hz, J_2 = 10.0 Hz), 1.83 (3H, s).

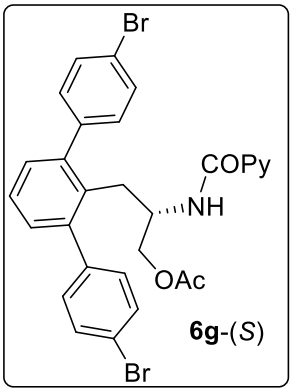
$^{13}C\{^1H\}$ NMR (~101 MHz, $CDCl_3$): δ_C 170.5, 163.3, 149.3, 147.7, 142.3, 140.6, 137.2, 132.4, 131.4, 131.3, 129.7, 126.4, 126.2, 122.1, 121.3, 65.4, 48.6, 31.1, 20.6.

HRMS (ESI): *m/z* $(M + H)^+$ calcd for $C_{29}H_{25}Br_2N_2O_3$: 607.0232 found: 607.0251.

$(\alpha)^{25}_D$ = 34.9 (*c* = 0.02 g/mL, $CHCl_3$).

The enantiomeric ratio (*er* 98:2) of compound **6g**-(R) was determined by using the Daicel Chiralpak IC column, hexane/*i*-PrOH 50:50, flow rate 1.0 mL/min, UV detection at 254 nm, t_R = 9.93 min, t_S = 13.79 min.

(S)-3-(4,4''-Dibromo-(1,1':3',1''-terphenyl)-2'-yl)-2-(picolinamido)propyl acetate (6g-(S)):



Compound **6g**-(S) was obtained from procedure C after purification by column chromatography on silica gel (EtOAc:hexanes = 40:60) as a colourless solid (100 mg, 66%, 0.25 mmol scale). R_f (EtOAc/hexanes = 40:60) 0.6. mp: 131-133 ^oC.

IR (DCM): 3378, 1740, 1517 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ_H 8.55 (1H, d, J = 4.2 Hz), 8.01 (1H, d, J = 7.8 Hz), 7.80 (1H, td, J_1 = 7.7 Hz, J_2 = 1.7 Hz), 7.55 (4H, d, J = 8.4 Hz), 7.46-7.42 (2H, m), 7.26-7.22 (5H, m), 7.11 (2H, d, J = 7.5 Hz), 4.12-4.06 (1H, m), 3.72 (1H, dd, J_1 = 11.0 Hz, J_2 = 4.4 Hz), 3.65 (1H, dd, J_1 = 11.1 Hz, J_2 = 5.4 Hz), 3.06 (1H, dd, J_1 = 14.1 Hz, J_2 = 4.7 Hz), 2.97 (1H, dd, J_1 = 14.1 Hz, J_2 = 10.0 Hz), 1.83 (3H, s).

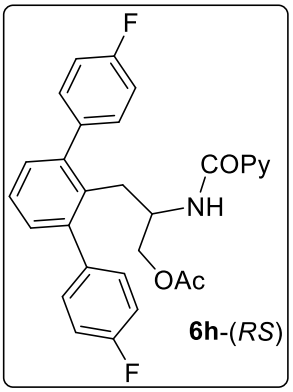
$^{13}C\{^1H\}$ NMR (~101 MHz, $CDCl_3$): δ_C 170.6, 163.4, 149.3, 147.8, 142.4, 140.7, 137.3, 132.5, 131.5, 131.4, 129.8, 126.5, 126.3, 122.3, 121.4, 65.5, 48.7, 31.1, 20.6.

$(\alpha)^{25}_D$ = -38.9 (c = 0.02 g/mL, $CHCl_3$).

HRMS (ESI): m/z $(M + H)^+$ calcd for $C_{29}H_{25}Br_2N_2O_3$: 607.0232 found: 607.0235.

The enantiomeric ratio (*er* 98:2) of compound **6g**-(S) was determined by using the Daicel Chiralpak IC column, hexane/*i*-PrOH 50:50, flow rate 1.0 mL/min, UV detection at 254 nm, t_R = 10.29 min, t_S = 14.16 min.

3-(4,4''-Difluoro-(1,1':3',1''-terphenyl)-2'-yl)-2-(picolinamido)propyl acetate (6h-(RS)):



Compound **6h**-(RS) was obtained from procedure C after purification by column chromatography on silica gel (EtOAc:hexanes = 40:60) as a colourless solid (75 mg, 62%, 0.25 mmol scale). R_f(EtOAc/hexanes = 40:60) 0.6. mp: 104-106 ^oC.

IR (DCM): 3376, 1739, 1511 cm^{-1}.

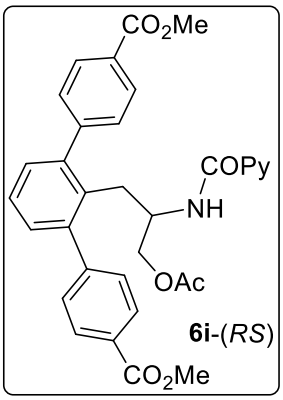
^1H NMR (400 MHz, $CDCl_3$): δ_H 8.54 (1H, d, J = 4.3 Hz), 8.02 (1H, d, J = 7.8 Hz), 7.79 (1H, td, J_1 = 7.7 Hz, J_2 = 1.6 Hz), 7.47 (1H, d, J = 9.5 Hz), 7.43-7.40 (1H, m), 7.36-7.32 (4H, m), 7.25-7.21 (1H, m), 7.14-7.10 (6H, m), 4.13-4.05 (1H, m), 3.72-3.64 (2H, m), 3.06 (1H, dd, J_1 = 14.1 Hz, J_2 = 5.1 Hz), 2.99 (1H, dd, J_1 = 14.1 Hz, J_2 = 9.7 Hz), 1.81 (3H, s).

$^{13}C\{^{1}H\}$ NMR (~101 MHz, $CDCl_3$): δ_C 170.6, 163.5, 162.0 (d, J_{C-F} = 244.5 Hz), 149.4, 147.8, 142.6, 137.8 (d, J_{C-F} = 3.3 Hz), 137.3, 132.9, 131.3, 131.3, 129.9, 126.3 (d, J_{C-F} = 13.5 Hz), 122.3, 115.2 (d, J_{C-F} = 21.2 Hz), 65.6, 48.5, 31.2, 20.6.

$^{19}F\{^{1}H\}$ NMR (~376 MHz, $CDCl_3$): δ_F = -115.42.

HRMS (ESI): *m/z* $(M + H)^+$ calcd for $C_{29}H_{25}F_2N_2O_3$: 487.1833 found: 487.1852.

Dimethyl 2'-(3-acetoxy-2-(picolinamido)propyl)-(1,1':3',1''-terphenyl)-4,4''-dicarboxylate (6i-(RS)):



Compound **6i**-(RS) was obtained from procedure C after purification by column chromatography on silica gel (EtOAc:hexanes = 40:60) as a colourless semi-solid (74 mg, 52%, 0.25 mmol scale). R_f (EtOAc/hexanes = 40:60) 0.3.

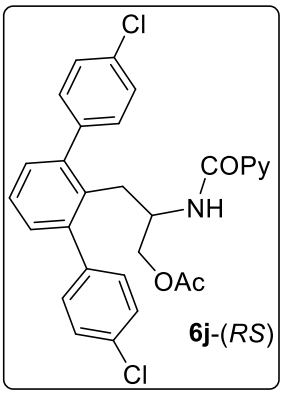
IR (DCM): 3358, 1727, 1519 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ_H 8.54 (1H, d, *J* = 4.6 Hz), 8.12 (4H, d, *J* = 8.3 Hz), 8.00 (1H, d, *J* = 7.8 Hz), 7.80 (1H, td, J_1 = 7.7 Hz, J_2 = 1.4 Hz), 7.46 (4H, d, *J* = 8.1 Hz), 7.45-7.42 (2H, m), 7.28 (1H, t, *J* = 8.2 Hz), 7.16 (2H, d, *J* = 7.6 Hz), 4.09-4.03 (1H, m), 3.97 (6H, s), 3.66 (1H, dd, J_1 = 11.1 Hz, J_2 = 4.6 Hz), 3.61 (1H, dd, J_1 = 11.1 Hz, J_2 = 5.2 Hz), 3.10 (1H, dd, J_1 = 14.2 Hz, J_2 = 4.6 Hz), 3.00 (1H, dd, J_1 = 14.2 Hz, J_2 = 10.1 Hz), 1.76 (3H, s).

$^{13}C\{^{1}H\}$ NMR (~101 MHz, $CDCl_3$): δ_C 170.4, 166.8, 163.3, 149.2, 147.7, 146.5, 142.6, 137.2, 132.2, 129.7, 129.6, 128.9, 126.4, 126.2, 122.1, 65.4, 52.1, 48.5, 31.2, 20.5.

HRMS (ESI): *m/z* $(M + H)^+$ calcd for $C_{33}H_{31}N_2O_7$: 567.2131 found: 567.2142.

3-(4,4''-Dichloro-(1,1':3',1''-terphenyl)-2'-yl)-2-(picolinamido)propyl acetate (6j-(RS)):



Compound **6j**-(RS) was obtained from procedure C after purification by column chromatography on silica gel (EtOAc:hexanes = 40:60) as a colourless solid (55 mg, 53%, 0.20 mmol scale). R_f (EtOAc/hexanes = 40:60) 0.6. mp: 120-122 °C.

IR (DCM): 3374, 1740, 1509 cm^{-1}.

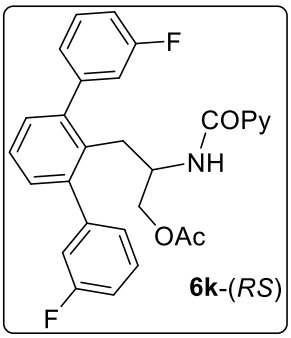
^{1}H NMR (400 MHz, $CDCl_3$): δ_H 8.54 (1H, d, *J* = 4.6 Hz), 8.00 (1H, d, *J* = 7.8 Hz), 7.80 (1H, td, J_1 = 7.6 Hz, J_2 = 1.5 Hz), 7.46-7.39 (6H, m), 7.30 (4H, d, *J* = 8.3 Hz), 7.25-7.21 (1H, m), 7.11 (2H, d, *J* = 7.6 Hz), 4.13-4.05 (1H, m), 3.72 (1H, dd, J_1 = 11.0 Hz, J_2 = 4.4 Hz), 3.65 (1H, dd, J_1 = 11.1 Hz, J_2 = 5.4

Hz), 3.06 (1H, dd, J_1 = 14.2 Hz, $J_{2=}$ 4.8 Hz), 2.97 (1H, dd, J_1 = 14.1 Hz, $J_{2=}$ 9.9 Hz), 1.82 (3H, s).

$^{13}C\{^1H\}$ NMR (~126 MHz, $CDCl_3$): δ_C 170.5, 163.4, 149.4, 147.8, 142.4, 140.3, 137.3, 133.2, 132.7, 131.1, 129.9, 128.5, 126.4, 126.2, 122.2, 65.6, 48.7, 31.2, 20.5.

HRMS (ESI): *m/z* $(M + H)^+$ calcd for $C_{29}H_{25}Cl_2N_2O_3$: 519.1242 found: 519.1262.

3-(3,3''-Difluoro-(1,1':3',1''-terphenyl)-2'-yl)-2-(picolinamido)propyl acetate (6k-(RS)):



Compound **6k**-(RS) was obtained from procedure C after purification by column chromatography on silica gel (EtOAc:hexanes = 40:60) as a yellow coloured semi-solid (80 mg, 66%, 0.25 mmol scale). R_f (EtOAc/hexanes = 40:60) 0.65.

IR (DCM): 3377, 1743, 1518 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ_H 8.56 (1H, d, J = 4.5 Hz), 8.01 (1H, d, J = 7.8 Hz), 7.79 (1H, td, J_1 = 7.7 Hz, J_2 = 1.6 Hz), 7.49 (1H, d, J = 9.5 Hz), 7.45-7.39 (3H, m), 7.26-7.23 (1H, m), 7.19-7.08 (8H, m), 4.15-4.07 (1H, m), 3.71 (1H, dd, J_1 = 11.0 Hz, J_2 = 4.5 Hz), 3.67 (1H, dd, J_1 = 11.1 Hz, J_2 = 5.4 Hz), 3.12 (1H, dd, J_1 = 14.2 Hz, J_2 = 4.7 Hz), 3.01 (1H, dd, J_1 = 14.2 Hz, J_2 = 10.2 Hz), 1.82 (3H, s).

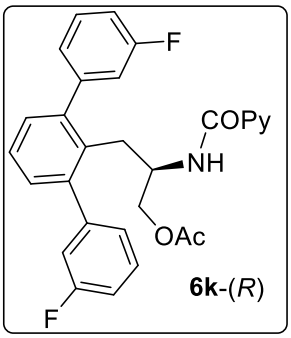
$^{13}C\{^1H\}$ NMR (~101 MHz, $CDCl_3$): δ_C 170.6, 163.5, 162.6 (d, J_{C-F} = 245.1 Hz), 149.3, 148.0, 143.9 (d, J_{C-F} = 7.4 Hz), 142.4, 137.2, 132.4, 129.8, 129.8 (d, J_{C-F} = 8.1 Hz), 126.4, 126.2, 125.6 (d, J_{C-F} = 2.6 Hz), 122.2, 116.8 (d, J_{C-F} = 21.3 Hz), 114.1 (d, J_{C-F} = 20.9 Hz), 65.6, 48.5, 31.2, 20.6.

$^{19}F\{^1H\}$ NMR (~376 MHz, $CDCl_3$): δ_F = -112.73.

HRMS (ESI): *m/z* $(M + H)^+$ calcd for $C_{29}H_{25}F_2N_2O_3$: 487.1833 found: 487.1846.

The HPLC of compound **6k**-(RS) was determined by using the Daicel Chiralpak IC column, hexane/*i*-PrOH 60:40, flow rate 1.0 mL/min, UV detection at 254 nm, t_R = 8.17 min, t_S = 10.79 min.

(R)-3-(3,3''-Difluoro-(1,1':3',1''-terphenyl)-2'-yl)-2-(picolinamido)propyl acetate (6k-(R)):



Compound **6k**-(R) was obtained from procedure C after purification by column chromatography on silica gel (EtOAc:hexanes = 40:60) as a yellow coloured semi-solid (78 mg, 64%, 0.25 mmol scale). R_f (EtOAc/hexanes = 40:60) 0.65.

IR (DCM): 3367, 1742, 1518 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ_H 8.56 (1H, d, J = 4.4 Hz), 8.01 (1H, d, J = 7.8 Hz), 7.79 (1H, td, J_1 = 7.7 Hz, J_2 = 1.6 Hz), 7.49 (1H, d, J = 9.5 Hz), 7.45-7.39 (3H, m), 7.26-7.23 (1H, m), 7.19-7.08 (8H, m), 4.14-4.07 (1H, m), 3.71 (1H, dd, J_1 = 11.0 Hz, J_2 = 4.5 Hz), 3.66 (1H, dd, J_1 = 11.1 Hz, J_2 = 5.4 Hz), 3.11 (1H, dd, J_1 = 14.2 Hz, J_2 = 4.7 Hz), 3.01 (1H, dd, J_1 = 14.2 Hz, J_2 = 10.2 Hz), 1.82 (3H, s).

$^{13}C\{^1H\}$ NMR (~101 MHz, $CDCl_3$): δ_C 170.5, 163.4, 162.5 (d, J_{C-F} = 245.2 Hz), 149.2, 147.9, 143.9 (d, J_{C-F} = 7.4 Hz), 142.3, 137.2, 132.3, 129.8, 129.8 (d, J_{C-F} = 7.8 Hz), 126.4, 126.1, 125.5 (d, J_{C-F} = 2.7 Hz), 122.1, 116.7 (d, J_{C-F} = 21.3 Hz), 114.0 (d, J_{C-F} = 20.8 Hz), 65.5, 48.4, 31.1, 20.5.

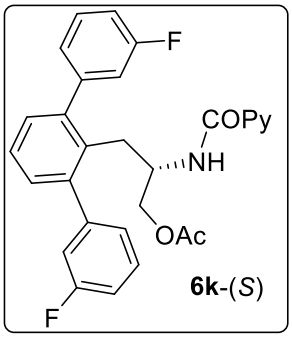
$^{19}F\{^1H\}$ NMR (~376 MHz, $CDCl_3$): δ_F = -112.71.

HRMS (ESI): *m/z* $(M + H)^+$ calcd for $C_{29}H_{25}F_2N_2O_3$: 487.1833 found: 487.1840.

$(\alpha)^{25}_D$ = 56.6 (c = 0.03 g/mL, $CHCl_3$).

The enantiomeric ratio (*er* 97:3) of compound **6k**-(R) was determined by using the Daicel Chiralpak IC column, hexane/*i*-PrOH 60:40, flow rate 1.0 mL/min, UV detection at 254 nm, t_R = 8.21 min, t_S = 10.86 min.

(S)-3-(3,3''-Difluoro-(1,1':3',1''-terphenyl)-2'-yl)-2-(picolinamido)propyl acetate (6k-(S)):



Compound **6k**-(S) was obtained from procedure C after purification by column chromatography on silica gel (EtOAc:hexanes = 40:60) as a yellow coloured semi-solid (77 mg, 63%, 0.25 mmol scale). R_f (EtOAc/hexanes = 40:60) 0.65.

IR (DCM): 3370, 1742, 1517 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ_H 8.56 (1H, d, J = 4.5 Hz), 8.01 (1H, d, J = 7.8 Hz), 7.78 (1H, td, J_1 = 7.6 Hz, J_2 = 1.4 Hz), 7.50 (1H, d, J = 9.4 Hz), 7.44-7.39 (3H, m), 7.24-7.22 (1H, m), 7.19-7.08 (8H, m), 4.14-4.08 (1H, m), 3.72 (1H, dd, J_1 = 11.1 Hz, J_2 =

4.5 Hz), 3.67 (1H, dd, J_1 = 11.0 Hz, J_2 = 5.4 Hz), 3.12 (1H, dd, J_1 = 14.2 Hz, J_2 = 4.6 Hz), 3.01 (1H, dd, J_1 = 14.2 Hz, J_2 = 10.2 Hz), 1.82 (3H, s).

$^{13}C\{^1H\}$ NMR (~126 MHz, $CDCl_3$): δ_C 170.5, 163.5, 162.6 (d, J_{C-F} = 245.2 Hz), 149.4, 148.0, 143.9 (d, J_{C-F} = 7.7 Hz), 142.4, 137.2, 132.4, 129.9 (d, J_{C-F} = 7.9 Hz), 129.8, 126.4, 126.2, 125.6 (d, J_{C-F} = 2.7 Hz), 122.2, 116.8 (d, J_{C-F} = 21.2 Hz), 114.1 (d, J_{C-F} = 20.5 Hz), 65.6, 48.5, 31.2, 20.5.

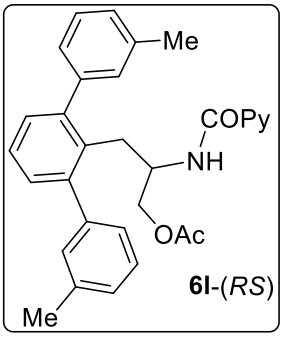
$^{19}F\{^1H\}$ NMR (~376 MHz, $CDCl_3$): δ_F = -112.70.

HRMS (ESI): *m/z* $(M + H)^+$ calcd for $C_{29}H_{25}F_2N_2O_3$: 487.1833 found: 487.1840.

$(\alpha)^{25}_D$ = -69.9 (*c* = 0.03 g/mL, $CHCl_3$).

The enantiomeric ratio (*er* 98:2) of compound **6k**-(S) was determined by using the Daicel Chiralpak IC column, hexane/*i*-PrOH 60:40, flow rate 1.0 mL/min, UV detection at 254 nm, t_R = 8.10 min, t_S = 10.65 min.

3-(3,3''-Dimethyl-(1,1':3',1''-terphenyl)-2'-yl)-2-(picolinamido)propyl acetate (6l-(RS)):



Compound **6l**-(RS) was obtained from procedure C after purification by column chromatography on silica gel (EtOAc:hexanes = 40:60) as a brown coloured semi-solid (84 mg, 70%, 0.25 mmol scale). R_f (EtOAc/hexanes = 40:60) 0.55.

IR (DCM): 3377, 1740, 1514 cm^{-1}.

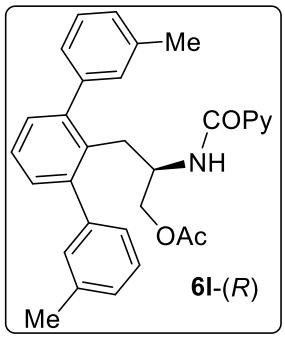
^1H NMR (400 MHz, $CDCl_3$): δ_H 8.53 (1H, d, *J* = 4.3 Hz), 8.03 (1H, d, *J* = 7.8 Hz), 7.78 (1H, td, J_1 = 7.7 Hz, J_2 = 1.6 Hz), 7.48 (1H, d, *J* = 9.2 Hz), 7.41-7.37 (1H, m), 7.34-7.30 (2H, m), 7.26-7.17 (7H, m), 7.13 (2H, d, *J* = 7.6 Hz), 4.15-4.07 (1H, m), 3.69 (1H, dd, J_1 = 11.0 Hz, J_2 = 4.5 Hz), 3.64 (1H, dd, J_1 = 11.0 Hz, J_2 = 4.9 Hz), 3.12 (1H, dd, J_1 = 14.0 Hz, J_2 = 5.2 Hz), 3.04 (1H, dd, J_1 = 14.0 Hz, J_2 = 9.7 Hz), 2.40 (6H, s), 1.77 (3H, s).

$^{13}C\{^1H\}$ NMR (~101 MHz, $CDCl_3$): δ_C 170.5, 163.4, 149.7, 147.7, 143.6, 142.0, 137.7, 137.1, 132.5, 130.2, 129.4, 128.1, 127.6, 126.7, 126.0, 125.9, 122.2, 65.6, 48.5, 31.1, 21.5, 20.5.

HRMS (ESI): *m/z* $(M + H)^+$ calcd for $C_{31}H_{31}N_2O_3$: 479.2335 found: 479.2344.

The HPLC of compound **6l**-(RS) was determined by using the Daicel Chiralpak IC column, hexane/*i*-PrOH 50:50, flow rate 1.0 mL/min, UV detection at 254 nm, t_R = 7.17 min, t_S = 9.51 min.

(R)-3-(3,3''-Dimethyl-(1,1':3',1''-terphenyl)-2'-yl)-2-(picolinamido)propylacetate(6l-(R)):



Compound **6l**-(R) was obtained from procedure C after purification by column chromatography on silica gel (EtOAc:hexanes = 40:60) as a brown coloured semi-solid (73 mg, 61%, 0.25 mmol scale). R_f (EtOAc/hexanes = 40:60) 0.55.

IR (DCM): 3386, 1741, 1513 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ_H 8.53 (1H, d, J = 4.4 Hz), 8.03 (1H, d, J = 7.8 Hz), 7.78 (1H, td, J_1 = 7.7 Hz, J_2 = 1.4 Hz), 7.48 (1H, d, J = 9.3 Hz), 7.41-7.38 (1H, m), 7.34-7.30 (2H, m), 7.26-7.17 (7H, m), 7.13 (2H, d, J = 7.4 Hz), 4.14-4.08 (1H, m), 3.69 (1H, dd, J_1 = 11.0 Hz, J_2 = 4.5 Hz), 3.64 (1H, dd, J_1 = 11.0 Hz, J_2 = 4.9 Hz), 3.12 (1H, dd, J_1 = 14.0 Hz, J_2 = 5.2 Hz), 3.04 (1H, dd, J_1 = 14.0 Hz, J_2 = 9.7 Hz), 2.40 (6H, s), 1.77 (3H, s).

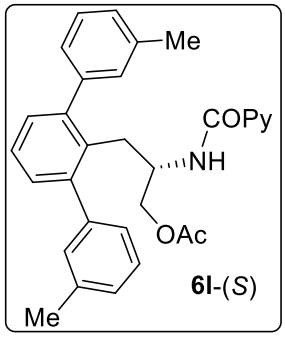
$^{13}C\{^1H\}$ NMR (~101 MHz, $CDCl_3$): δ_C 170.6, 163.4, 149.6, 147.7, 143.6, 142.0, 137.8, 137.1, 132.5, 130.2, 129.4, 128.1, 127.6, 126.7, 126.0, 125.9, 122.2, 65.5, 48.5, 31.1, 21.5, 20.5.

HRMS (ESI): m/z $(M + H)^+$ calcd for $C_{31}H_{31}N_2O_3$: 479.2335 found: 479.2336.

$(\alpha)^{25}_D$ = 61.1 (c = 0.02 g/mL, $CHCl_3$).

The enantiomeric ratio (*er* 96:4) of compound **6l**-(R) was determined by using the Daicel Chiralpak IC column, hexane/*i*-PrOH 50:50, flow rate 1.0 mL/min, UV detection at 254 nm, t_R = 7.09 min, t_S = 9.38 min.

(S)-3-(3,3''-Dimethyl-(1,1':3',1''-terphenyl)-2'-yl)-2-(picolinamido)propyl acetate (6l-(S)):



Compound **6l**-(S) was obtained from procedure C after purification by column chromatography on silica gel (EtOAc:hexanes = 40:60) as a brown coloured semi-solid (81 mg, 68%, 0.25 mmol scale). R_f (EtOAc/hexanes = 40:60) 0.55.

IR (DCM): 3381, 1740, 1513 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ_H 8.53 (1H, d, J = 4.2 Hz), 8.03 (1H, d, J = 7.8 Hz), 7.77 (1H, td, J_1 = 7.7 Hz, J_2 = 1.6 Hz), 7.48 (1H, d, J = 9.3 Hz), 7.40-7.37 (1H, m), 7.34-7.30 (2H, m), 7.24-7.17 (7H, m), 7.13 (2H, d, J = 7.2 Hz), 4.14-4.08 (1H, m), 3.69 (1H, dd, J_1 = 11.0 Hz, J_2 = 4.5 Hz), 3.64 (1H, dd, J_1 = 11.0 Hz, J_2 = 4.9 Hz), 3.13 (1H, dd, J_1 = 14.0 Hz, J_2 = 5.2 Hz), 3.04 (1H, dd, J_1 = 14.0 Hz, J_2 = 9.7 Hz), 2.40 (6H, s), 1.77 (3H, s).

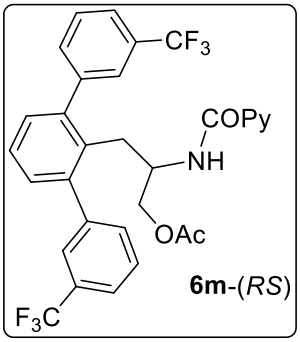
$^{13}C\{^{1}H\}$ NMR (~126 MHz, $CDCl_3$): δ_C 170.6, 163.5, 149.8, 147.8, 143.7, 142.1, 137.8, 137.2, 132.6, 130.3, 129.5, 128.2, 127.7, 126.8, 126.1, 126.0, 122.3, 65.7, 48.7, 31.2, 21.5, 20.6.

HRMS (ESI): *m/z* $(M + H)^+$ calcd for $C_{31}H_{31}N_2O_3$: 479.2335 found: 479.2350.

$(\alpha)^{25}_D$ = -60.1 (*c* = 0.02 g/mL, $CHCl_3$).

The enantiomeric ratio (*er* 96:4) of compound **6l**-(S) was determined by using the Daicel Chiralpak IC column, hexane/*i*-PrOH 50:50, flow rate 1.0 mL/min, UV detection at 254 nm, t_R = 7.23 min, t_S = 9.61 min.

3-(3,3''-Bis(trifluoromethyl)-(1,1':3',1''-terphenyl)-2'-yl)-2-(picolinamido)propyl acetate (6m-(RS)):



Compound **6m**-(RS) was obtained from procedure C after purification by column chromatography on silica gel (EtOAc:hexanes = 40:60) as a yellow coloured semi-solid (125 mg, 70%, 0.30 mmol scale). R_f (EtOAc/hexanes = 40:60) 0.6.

IR (DCM): 3386, 1743, 1516 cm^{-1}.

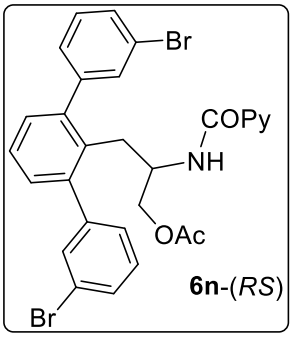
^{1}H NMR (400 MHz, $CDCl_3$): δ_H 8.54 (1H, dd, J_1 = 4.1 Hz, J_2 = 0.8 Hz), 8.00 (1H, d, *J* = 7.8 Hz), 7.79 (1H, td, J_1 = 7.7 Hz, J_2 = 1.6 Hz), 7.68-7.57 (8H, m), 7.48 (1H, d, *J* = 9.7 Hz), 7.43-7.40 1H, m), 7.30-7.28 (1H, m), 7.16 (2H, d, *J* = 7.7 Hz), 4.11-4.05 (1H, m), 3.68 (1H, dd, J_1 = 11.1 Hz, J_2 = 4.4 Hz), 3.63 (1H, dd, J_1 = 11.1 Hz, J_2 = 5.1 Hz), 3.06 (1H, dd, J_1 = 14.2 Hz, J_2 = 4.9 Hz), 2.97 (1H, dd, J_1 = 14.2 Hz, J_2 = 10.3 Hz), 1.76 (3H, s).

$^{13}C\{^{1}H\}$ NMR (~126 MHz, $CDCl_3$): δ_C 170.3, 163.3, 149.2, 147.9, 142.5, 142.3, 142.3, 137.2, 133.4, 132.4, 130.6 (q, J_{C-F} = 31.9 Hz), 130.1, 128.9, 126.6, 126.1 (q, J_{C-F} = 3.9 Hz), 124.1 (q, J_{C-F} = 270.7 Hz), 124.0 (q, J_{C-F} = 3.9 Hz), 122.1, 65.5, 48.0, 31.3, 20.2.

$^{19}F\{^{1}H\}$ NMR (~376 MHz, $CDCl_3$): δ_F = -62.31.

HRMS (ESI): *m/z* $(M + H)^+$ calcd for $C_{31}H_{25}F_6N_2O_3$: 587.1769 found: 587.1786.

3-(3,3''-Dibromo-(1,1':3',1''-terphenyl)-2'-yl)-2-(picolinamido)propyl acetate (6n-(RS)):



Compound **6n**-(RS) was obtained from procedure C after purification by column chromatography on silica gel (EtOAc:hexanes = 40:60) as a yellow coloured semi-solid (85 mg, 56%, 0.25 mmol scale). R_f (EtOAc/hexanes = 40:60) 0.6.

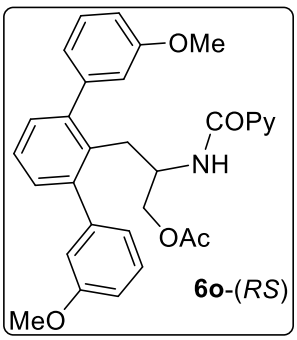
IR (DCM): 3380, 1740, 1513 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ_H 8.63 (1H, d, J = 4.4 Hz), 8.01 (1H, d, J = 7.8 Hz), 7.79 (1H, t, J = 7.6 Hz), 7.57-7.50 (5H, m), 7.43-7.40 (1H, m), 7.34-7.30 (4H, m), 7.25-7.21 (1H, m), 7.12 (2H, d, J = 7.6 Hz), 4.15-4.09 (1H, m), 3.74 (1H, dd, J_1 = 11.0 Hz, $J_{2=}$ 4.3 Hz), 3.68 (1H, dd, J_1 = 11.0 Hz, $J_{2=}$ 5.3 Hz), 3.10 (1H, dd, J_1 = 14.1 Hz, $J_{2=}$ 4.6 Hz), 2.99 (1H, dd, J_1 = 14.0 Hz, $J_{2=}$ 10.3 Hz), 1.84 (3H, s).

$^{13}C\{^1H\}$ NMR (~101 MHz, $CDCl_3$): δ_C 170.5, 163.4, 149.2, 148.1, 143.8, 142.1, 137.2, 132.3, 130.2, 129.9, 128.5, 126.4, 126.1, 122.3, 122.1, 65.5, 48.3, 31.2, 20.6.

HRMS (ESI): *m/z* $(M + H)^+$ calcd for $C_{29}H_{25}Br_2N_2O_3$: 607.0232 found: 607.0238.

3-(3,3''-Dimethoxy-(1,1':3',1''-terphenyl)-2'-yl)-2-(picolinamido)propyl acetate (6o-(RS)):



Compound **6o**-(RS) was obtained from procedure C after purification by column chromatography on silica gel (EtOAc:hexanes = 40:60) as a yellow coloured semi-solid (90 mg, 71%, 0.25 mmol scale). R_f (EtOAc/hexanes = 40:60) 0.3.

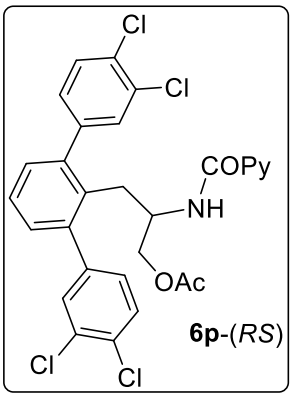
IR (DCM): 3371, 1740, 1515 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ_H 8.53 (1H, d, J = 4.5 Hz), 8.01 (1H, d, J = 7.8 Hz), 7.76 (1H, t, J = 7.6 Hz), 7.51 (1H, d, J = 9.2 Hz), 7.40-7.33 (3H, m), 7.25-7.21 (1H, m), 7.16 (2H, d, J = 7.5 Hz), 6.98-6.92 (6H, m), 4.18-4.10 (1H, m), 3.83 (6H, s), 3.73-3.65 (2H, m), 3.14 (1H, dd, J_1 = 14.1 Hz, J_2 = 5.4 Hz), 3.08 (1H, dd, J_1 = 14.1 Hz, J_2 = 9.8 Hz), 1.79 (3H, s).

$^{13}C\{^1H\}$ NMR (~76 MHz, $CDCl_3$): δ_C 170.6, 163.5, 159.5, 149.7, 147.9, 143.4, 143.3, 137.1, 132.6, 129.6, 129.3, 126.1, 125.9, 122.1, 115.3, 112.7, 65.6, 55.3, 48.6, 31.2, 20.5.

HRMS (ESI): *m/z* $(M + H)^+$ calcd for $C_{31}H_{31}N_2O_5$: 511.2233 found: 511.2257.

2-(Picolinamido)-3-(3,3'',4,4''-tetrachloro-(1,1':3',1''-terphenyl)-2'-yl)propyl acetate (6p-(RS)):



Compound **6p**-(RS) was obtained from procedure C after purification by column chromatography on silica gel (EtOAc:hexanes = 40:60) as a colourless solid (70 mg, 60%, 0.20 mmol scale). R_f(EtOAc/hexanes = 40:60) 0.6. mp: 130-132 ^oC.

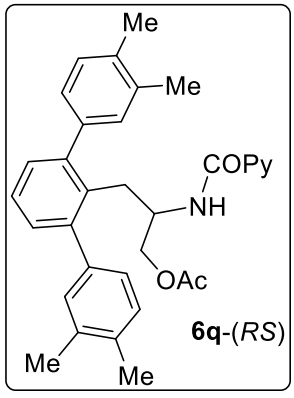
IR (DCM): 3383, 1742, 1517 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ_H 8.53 (1H, dd, J_1 = 4.7 Hz, J_2 = 0.6 Hz), 7.92 (1H, d, J = 7.8 Hz), 7.73 (1H, td, J_1 = 7.7 Hz, J_2 = 1.7 Hz), 7.46-7.40 (5H, m), 7.38-7.34 (1H, m), 7.19-7.15 (3H, m), 7.04 (2H, d, J = 7.5 Hz), 4.09-4.01 (1H, m), 3.70 (1H, dd, J_1 = 11.1 Hz, J_2 = 4.4 Hz), 3.61 (1H, dd, J_1 = 11.0 Hz, J_2 = 5.8 Hz), 3.00 (1H, dd, J_1 = 14.2 Hz, J_2 = 4.4 Hz), 2.88 (1H, dd, J_1 = 14.2 Hz, J_2 = 10.5 Hz), 1.78 (3H, s).

$^{13}C\{^1H\}$ NMR (~101 MHz, $CDCl_3$): δ_C 170.5, 163.5, 149.2, 148.2, 141.7, 141.4, 137.4, 132.5, 132.4, 131.6, 131.4, 130.4, 130.1, 129.3, 126.7, 126.3, 122.2, 65.6, 48.5, 31.3, 20.5.

HRMS (ESI): *m/z* $(M + H)^+$ calcd for $C_{29}H_{23}Cl_4N_2O_3$: 587.0463 found: 587.0461.

2-(Picolinamido)-3-(3,3'',4,4''-tetramethyl-(1,1':3',1''-terphenyl)-2'-yl)propyl acetate (6q-(RS)):



Compound **6q**-(RS) was obtained from procedure C after purification by column chromatography on silica gel (EtOAc:hexanes = 40:60) as a yellow coloured semi-solid (71 mg, 56%, 0.25 mmol scale). R_f(EtOAc/hexanes = 40:60) 0.6.

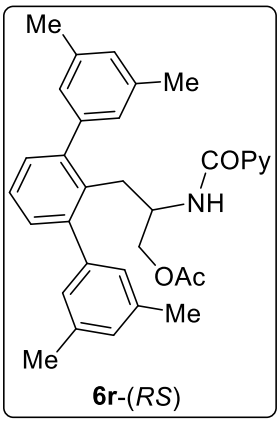
IR (DCM): 3389, 1742, 1516 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ_H 8.53 (1H, dd, J_1 = 4.7 Hz, J_2 = 0.7 Hz), 8.03 (1H, d, J = 7.8 Hz), 7.78 (1H, td, J_1 = 7.7 Hz, J_2 = 1.6 Hz), 7.46 (1H, d, J = 9.2 Hz), 7.41-7.38 (1H, m), 7.21-7.10 (9H, m), 4.14-4.08 (1H, m), 3.71 (1H, dd, J_1 = 11.0 Hz, J_2 = 4.6 Hz), 3.64 (1H, dd, J_1 = 11.0 Hz, J_2 = 5.1 Hz), 3.14 (1H, dd, J_1 = 14.0 Hz, J_2 = 5.0 Hz), 3.05 (1H, dd, J_1 = 14.0 Hz, J_2 = 9.8 Hz), 2.32 (6H, s), 2.29 (6H, s), 1.75 (3H, s).

$^{13}C\{^1H\}$ NMR (~101 MHz, $CDCl_3$): δ_C 170.6, 163.5, 149.8, 147.8, 143.6, 139.7, 137.2, 136.4, 135.1, 132.7, 130.8, 129.5, 129.5, 127.1, 126.0, 126.0, 122.3, 65.7, 48.8, 31.1, 20.5, 19.9, 19.5.

HRMS (ESI): *m/z* $(M + H)^+$ calcd for $C_{33}H_{35}N_2O_3$: 507.2648 found: 507.2667.

2-(Picolinamido)-3-(3,3'',5,5''-tetramethyl-(1,1':3',1''-terphenyl)-2'-yl)propyl acetate (6r-(RS)):



6r-(*RS*)

Compound **6r**-(RS) was obtained from procedure C after purification by column chromatography on silica gel (EtOAc:hexanes = 40:60) as a yellow coloured semi-solid (74 mg, 73%, 0.20 mmol scale). R_f (EtOAc/hexanes = 40:60) 0.65.

IR (DCM): 3383, 1742, 1514 cm^{-1}.

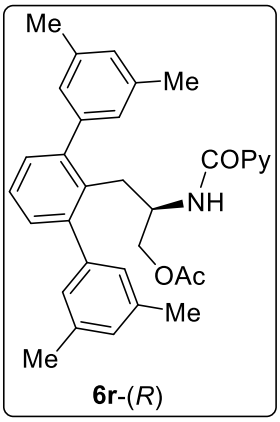
^1H NMR (400 MHz, $CDCl_3$): δ_H 8.52 (1H, d, J = 4.5 Hz), 8.04 (1H, d, J = 7.8 Hz), 7.77 (1H, t, J = 7.6 Hz), 7.49 (1H, d, J = 9.2 Hz), 7.39-7.36 (1H, m), 7.21-7.17 (1H, m), 7.11 (2H, d, J = 7.4 Hz), 7.01 (4H, s), 6.99 (2H, s), 4.17-4.12 (1H, m), 3.72 (1H, dd, J_1 = 11.0 Hz, $J_{2=}$ 4.2 Hz), 3.65 (1H, dd, J_1 = 11.0 Hz, $J_{2=}$ 4.6 Hz), 3.14 (1H, dd, J_1 = 14.0 Hz, $J_{2=}$ 4.9 Hz), 3.04 (1H, dd, J_1 = 14.0 Hz, $J_{2=}$ 9.7 Hz), 2.36 (12H, s), 1.77 (3H, s).

$^{13}C\{^1H\}$ NMR (~101 MHz, $CDCl_3$): δ_C 170.6, 163.4, 149.8, 147.8, 143.6, 142.0, 137.6, 137.1, 132.4, 129.3, 128.5, 127.3, 125.9, 125.9, 122.2, 65.6, 48.6, 31.2, 21.3, 20.4.

HRMS (ESI): *m/z* $(M + H)^+$ calcd for $C_{33}H_{35}N_2O_3$: 507.2648 found: 507.2649.

The HPLC of compound **6r**-(RS) was determined by using the Daicel Chiralpak IC column, hexane/*i*-PrOH 60:40, flow rate 1.0 mL/min, UV detection at 254 nm, t_R = 6.47 min, t_S = 9.08 min.

(R)-2-(Picolinamido)-3-(3,3'',5,5''-tetramethyl-(1,1':3',1''-terphenyl)-2'-yl)propyl acetate (6r-(R)):



6r-(*R*)

Compound **6r**-(R) was obtained from procedure C after purification by column chromatography on silica gel (EtOAc:hexanes = 40:60) as a yellow coloured semi-solid (80 mg, 63%, 0.25 mmol scale). R_f (EtOAc/hexanes = 40:60) 0.65.

IR (DCM): 3384, 1742, 1515 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ_H 8.53 (1H, dd, J_1 = 4.6 Hz, J_2 = 0.5 Hz), 8.04 (1H, d, J = 7.8 Hz), 7.78 (1H, td, J_1 = 7.7 Hz, J_2 = 1.6 Hz), 7.49 (1H, d, J = 9.3 Hz), 7.40-7.37 (1H, m), 7.21-7.17 (1H, m), 7.11 (2H, d, J = 7.2 Hz), 7.00 (4H, s), 6.99 (2H, s), 4.19-4.10 (1H, m), 3.72 (1H, dd, J_1 = 11.0 Hz, J_2 = 4.5 Hz), 3.65 (1H, dd, J_1 = 11.0 Hz, J_2 = 4.9 Hz), 3.14 (1H, dd, J_1 = 14.0 Hz, J_2 = 5.2 Hz), 3.04 (1H, dd, J_1 = 14.0 Hz, J_2 = 9.8 Hz), 2.36 (12H, s), 1.78 (3H, s).

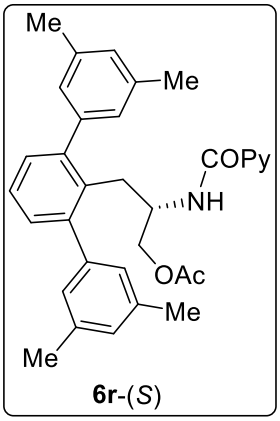
$^{13}C\{^{1}H\}$ NMR (~101 MHz, $CDCl_3$): δ_C 170.7, 163.5, 149.9, 147.9, 143.7, 142.1, 137.7, 137.2, 132.5, 129.4, 128.6, 127.4, 126.0, 125.9, 122.3, 65.7, 48.7, 31.3, 21.4, 20.5.

HRMS (ESI): *m/z* $(M + H)^+$ calcd for $C_{33}H_{35}N_2O_3$: 507.2648 found: 507.2651.

$(\alpha)^{25}_D$ = 51.1 (*c* = 0.02 g/mL, $CHCl_3$).

The enantiomeric ratio (*er* 96:4) of compound **6r**-(R) was determined by using the Daicel Chiralpak IC column, hexane/*i*-PrOH 60:40, flow rate 1.0 mL/min, UV detection at 254 nm, t_R = 6.54 min, t_S = 9.45 min.

(S)-2-(picolinamido)-3-(3,3'',5,5''-tetramethyl-(1,1':3',1''-terphenyl)-2'-yl)propyl acetate (6r-(S)):



6r-(*S*)

Compound **6r**-(S) was obtained from procedure C after purification by column chromatography on silica gel (EtOAc:hexanes = 40:60) as a yellow coloured semi-solid (73 mg, 72%, 0.20 mmol scale). R_f (EtOAc/hexanes = 40:60) 0.65.

IR (DCM): 3387, 1741, 1514 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ_H 8.46-8.45 (1H, m), 7.97 (1H, d, *J* = 7.8 Hz), 7.71 (1H, td, J_1 = 7.7 Hz, J_2 = 1.6 Hz), 7.41 (1H, d, *J* = 9.3 Hz), 7.33-7.30 (1H, m), 7.14-7.10 (1H, m), 7.03 (2H, d, *J* = 7.1 Hz), 6.93 (4H, s), 6.92 (2H, s), 4.10-4.04 (1H, m), 3.65 (1H, dd, J_1 = 11.0 Hz, J_2 = 4.5 Hz), 3.57 (1H, dd, J_1 =11.2 Hz, J_2 = 4.9 Hz), 3.10 (1H, dd, J_1 = 14.0 Hz, J_2 = 5.2 Hz), 2.96 (1H, dd, J_1 = 14.0 Hz, J_2 = 9.7 Hz), 2.28 (12H, s), 1.70 (3H, s).

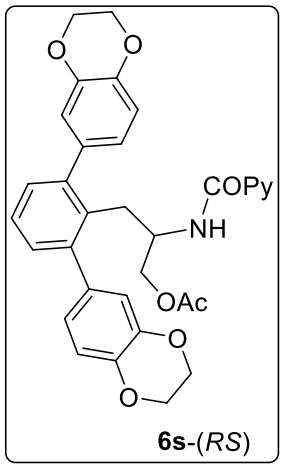
$^{13}C\{^{1}H\}$ NMR (~101 MHz, $CDCl_3$): δ_C 170.6, 163.5, 149.9, 147.9, 143.7, 142.1, 137.7, 137.2, 132.5, 129.4, 128.5, 127.4, 126.0, 125.9, 122.3, 65.7, 48.7, 31.3, 21.4, 20.5.

HRMS (ESI): *m/z* $(M + H)^+$ calcd for $C_{33}H_{35}N_2O_3$: 507.2648 found: 507.2647.

$(\alpha)^{25}_D$ = -52.1 (*c* = 0.02 g/mL, $CHCl_3$).

The enantiomeric ratio (*er* 97:3) of compound **6r**-(S) was determined by using the Daicel Chiralpak IC column, hexane/*i*-PrOH 60:40, flow rate 1.0 mL/min, UV detection at 254 nm, t_R = 6.03 min, t_S = 8.52 min.

3-(2,6-Bis(2,3-dihydrobenzo(*b*)(1,4)dioxin-6-yl)phenyl)-2-(picolinamido)propyl acetate (6s-(RS)):



Compound **6s**-(RS) was obtained from procedure C after purification by column chromatography on silica gel (EtOAc:hexanes = 40:60) as a yellow colour semi-solid (95 mg, 67%, 0.25 mmol scale). R_f (EtOAc/hexanes = 40:60) 0.2.

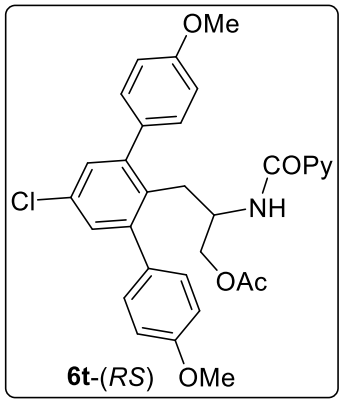
IR (DCM): 3372, 1738, 1509 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ_H 8.578.56 (1H, m), 8.02 (1H, d, J = 7.8 Hz), 7.78 (1H, td, J_1 = 7.7 Hz, J_2 = 1.7 Hz), 7.54 (1H, d, J = 9.2 Hz), 7.41-7.37 (1H, m), 7.20-7.16 (1H, m), 7.10 (2H, d, J = 7.0 Hz), 6.92-6.90 (4H, m), 6.85-6.82 (2H, m), 4.32 (8H, s), 4.15-4.09 (1H, m), 3.76 (1H, dd, J_1 = 11.0 Hz, J_2 = 4.6 Hz), 3.70 (1H, dd, J_1 = 11.0 Hz, J_2 = 5.2 Hz), 3.17 (1H, dd, J_1 = 14.1 Hz, J_2 = 5.2 Hz), 3.07 (1H, dd, J_1 = 14.0 Hz, J_2 = 9.8 Hz), 1.86 (3H, s).

$^{13}C\{^1H\}$ NMR (~101 MHz, $CDCl_3$): δ_C 170.5, 163.4, 149.5, 147.8, 143.2, 142.8, 142.6, 137.0, 135.3, 132.8, 129.5, 126.0, 125.9, 122.8, 122.0, 118.4, 116.9, 65.5, 64.3, 48.4, 31.0, 20.6.

HRMS (ESI): *m/z* $(M + H)^+$ calcd for $C_{33}H_{31}N_2O_7$: 567.2131 found: 567.2145.

3-(5'-Chloro-4,4''-dimethoxy-(1,1':3',1''-terphenyl)-2'-yl)-2-(picolinamido)propyl acetate (6t-(RS)):



Compound **6t**-(RS) was obtained from procedure C after purification by column chromatography on silica gel (EtOAc:hexanes = 50:50) as a colourless semi-solid (28 mg, 51%, 0.1 mmol scale). R_f (EtOAc/hexanes = 50:50) 0.4.

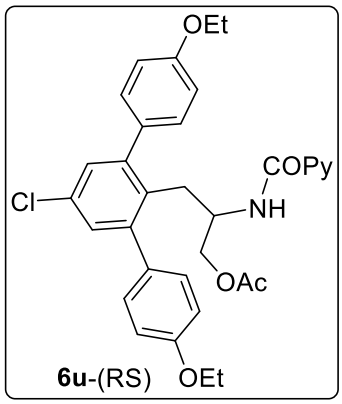
IR (DCM): 3430, 1743, 1516 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ_H 8.57-8.55 (1H, m), 8.05 (1H, d, J = 7.8 Hz), 7.82 (1H, td, J_1 = 7.7 Hz, J_2 = 1.7 Hz), 7.49-7.42 (2H, m), 7.29 (4H, d, J = 8.6 Hz), 7.13 (2H, s), 6.98 (4H, d, J = 8.7 Hz), 4.12-4.07 (1H, m), 3.89 (6H, s), 3.73 (1H, dd, J_1 = 11.0 Hz, J_2 = 4.6 Hz), 3.66 (1H, dd, J_1 = 11.0 Hz, J_2 = 5.1 Hz), 3.06 (1H, dd, J_1 = 14.1 Hz, J_2 = 5.1 Hz), 3.00 (1H, dd, J_1 = 14.1 Hz, J_2 = 9.8 Hz), 1.82 (3H, s).

$^{13}C\{^1H\}$ NMR (~101 MHz, $CDCl_3$): δ_C 170.6, 163.5, 158.9, 149.5, 147.7, 144.8, 137.3, 133.2, 131.9, 131.5, 130.6, 129.4, 126.2, 122.3, 113.8, 65.6, 55.3, 48.4, 30.7, 20.6.

HRMS (ESI): *m/z* $(M + H)^+$ calcd for $C_{31}H_{30}ClN_2O_5$: 545.1843; found: 545.1866.

3-(5'-Chloro-4,4''-diethoxy-(1,1':3',1''-terphenyl)-2'-yl)-2-(picolinamido)propyl acetate (6u-(RS)):



Compound **6u**-(RS) was obtained from procedure C after purification by column chromatography on silica gel (EtOAc:hexanes = 50:50) as a colourless semi-solid (24 mg, 42%, 0.10 mmol scale). R_f (EtOAc/hexanes = 50:50) 0.4.

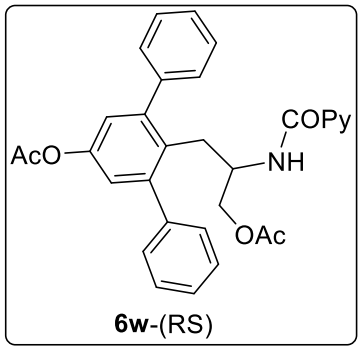
IR (DCM): 3384, 1742, 1511 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ_H 8.56 (1H, dd, J_1 = 4.6 Hz, J_2 = 0.6 Hz), 8.05 (1H, d, J = 7.8 Hz), 7.82 (1H, td, J_1 = 7.7 Hz, J_2 = 1.7 Hz), 7.48-7.42 (2H, m), 7.27 (4H, d, J = 8.8 Hz), 7.13 (2H, s), 6.97 (4H, d, J = 8.7 Hz), 4.14-4.07 (5H, m), 3.73 (1H, dd, J_1 = 11.1 Hz, J_2 = 4.6 Hz), 3.65 (1H, dd, J_1 = 11.0 Hz, J_2 = 5.1 Hz), 3.07 (dd, 1H, J_1 = 14.2 Hz, J_2 = 5.1 Hz), 3.00 (1H, dd, J_1 = 14.1 Hz, J_2 = 9.8 Hz), 1.82 (3H, s), 1.48 (6H, t, J = 7.0 Hz).

$^{13}C\{^1H\}$ NMR (~101 MHz, $CDCl_3$): δ_C 170.6, 163.5, 158.3, 149.5, 147.7, 144.8, 137.3, 133.0, 131.9, 131.5, 130.6, 129.3, 126.1, 122.3, 114.3, 65.7, 63.5, 48.4, 30.8, 20.6, 14.9.

HRMS (ESI): *m/z* $(M + H)^+$ calcd for $C_{33}H_{34}ClN_2O_5$: 573.2156 found: 573.2170.

2'-(3-Acetoxy-2-(picolinamido)propyl)-(1,1':3',1''-terphenyl)-5'-yl acetate (6w-(RS)):



Compound **6w-(RS)** was obtained from procedure C after purification by column chromatography on silica gel (EtOAc:hexanes = 50:50) as a colourless semi solid (13 mg, 25%, 0.1 mmol scale); R_f (EtOAc/hexanes = 50:50) 0.6;

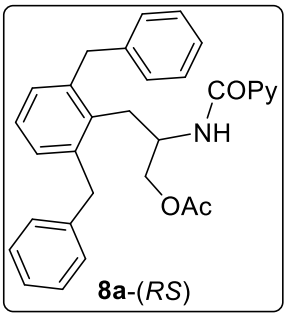
IR (DCM): 3376, 1740, 1514 cm^{-1};

^1H NMR (400 MHz, $CDCl_3$): δ_H 8.53 (1H, d, J = 4.3 Hz), 8.06 (1H, d, J = 7.7 Hz), 7.83 (1H, t, J = 7.3 Hz), 7.55 (1H, d, J = 9.2 Hz), 7.45-7.36 (11H, m), 6.93 (2H, s), 4.08-4.02 (1H, m), 3.64 (2H, d, J = 4.6 Hz), 3.12-3.00 (2H, m), 2.24 (3H, s), 1.76 (3H, s);

$^{13}C\{^1H\}$ NMR (~101 MHz, $CDCl_3$): δ_C 170.6, 169.3, 163.5, 149.6, 148.3, 147.7, 144.8, 141.1, 137.2, 130.4, 129.6, 128.4, 127.3, 126.1, 122.5, 122.3, 65.5, 48.4, 30.8, 21.1, 20.6.

HRMS (ESI): *m/z* $(M + H)^+$ calcd for $C_{31}H_{29}N_2O_5$: 509.2076; found: 509.2085.

3-(2,6-Dibenzylphenyl)-2-(picolinamido)propyl acetate (8a-(RS)):



Compound **8a**-(RS) was obtained from procedure D after purification by column chromatography on silica gel (EtOAc:hexanes = 40:60) as a colourless solid (50 mg, 70%, 0.15 mmol scale). R_f (EtOAc/hexanes = 40:60) 0.55. mp: 124-126 ºC.

IR (DCM): 3339, 1737, 1521 cm^{-1}.

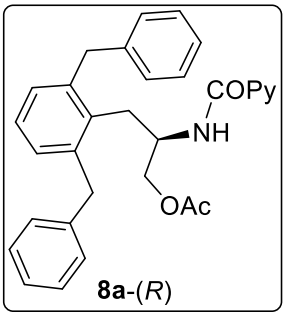
^1H NMR (400 MHz, $CDCl_3$): δ_H 8.56-8.54 (1H, m), 8.28 (1H, d, J = 9.1 Hz), 8.15 (1H, d, J = 7.8 Hz), 7.82 (1H, td, J_1 = 7.7 Hz, J_2 = 1.7 Hz), 7.43-7.39 (1H, m), 7.26-7.23 (4H, m), 7.18-7.15 (2H, m), 7.11-7.07 (5H, m), 6.97 (2H, d, J = 7.6 Hz), 4.72-4.66 (1H, m), 4.25-4.11 (6H, m), 3.07-2.95 (2H, m), 2.08 (3H, s).

$^{13}C\{^1H\}$ NMR (~101 MHz, $CDCl_3$): δ_C 170.8, 163.8, 149.5, 148.0, 140.8, 139.9, 137.3, 134.3, 129.3, 128.7, 128.4, 126.9, 126.2, 126.0, 122.2, 65.1, 49.1, 39.1, 31.2, 20.9.

HRMS (ESI): *m/z* $(M + H)^+$ calcd for $C_{31}H_{31}N_2O_3$: 479.2335 found: 479.2324.

The HPLC of compound **8a**-(RS) was determined by using the Daicel Chiralpak IA column, hexane/*i*-PrOH 90:10, flow rate 1.0 mL/min, UV detection at 254 nm, t_R = 13.53 min, t_S = 15.05 min.

(R)-3-(2,6-Dibenzylphenyl)-2-(picolinamido)propyl acetate (8a-(R)):



Compound **8a**-(R) was obtained from procedure D after purification by column chromatography on silica gel (EtOAc:hexanes = 40:60) as a colourless solid (67 mg, 56%, 0.25 mmol scale). R_f (EtOAc/hexanes = 40:60) 0.55. mp: 124-126 ºC.

IR (DCM): 3341, 1737, 1521 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ_H 8.56-8.54 (1H, m), 8.27 (1H, d, J = 9.2 Hz), 8.15 (1H, dt, J_1 = 2.0 Hz, $J_{2=}$ 1.0 Hz), 7.82 (1H, td, J_1 = 7.7 Hz, $J_{2=}$ 1.7 Hz), 7.43-7.40 (1H, m), 7.27-7.23 (4H, m), 7.19-7.15 (2H, m), 7.11-7.08 (5H, m), 6.97 (2H, d, J = 7.6 Hz), 4.73-4.64 (1H, m), 4.25-4.11 (6H, m), 3.06-2.95 (2H, m), 2.09 (3H, s).

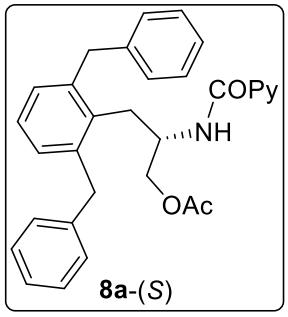
$^{13}C\{^1H\}$ NMR (~101 MHz, $CDCl_3$): δ_C 170.9, 163.8, 149.6, 148.1, 140.9, 140.0, 137.4, 134.4, 129.4, 128.8, 128.4, 127.0, 126.3, 126.0, 122.3, 65.2, 49.1, 39.2, 31.3, 21.0.

HRMS (ESI): *m/z* $(M + Na)^+$ calcd for $C_{31}H_{30}N_2NaO_3$: 501.2154 found: 501.2177.

$(\alpha)^{25}_D$ = 43.4 (c = 0.03 g/mL, $CHCl_3$).

The enantiomeric ratio (*er* 98:2) of compound **8a**-(R) was determined by using the Daicel Chiralpak IA column, hexane/*i*-PrOH 90:10, flow rate 1.0 mL/min, UV detection at 254 nm, t_R = 14.16 min, t_S = 16.76 min.

(S)-3-(2,6-Dibenzylphenyl)-2-(picolinamido)propyl acetate (8a-(S)):



Compound **8a**-(S) was obtained from procedure D after purification by column chromatography on silica gel (EtOAc:hexanes = 40:60) as a colourless solid (91 mg, 76%, 0.25 mmol scale). R_f (EtOAc/hexanes = 40:60) 0.55. mp: 126-128 ºC.

IR (DCM): 3330, 1737, 1521 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ_H 8.55 (1H, d, J = 4.7 Hz), 8.28 (1H, d, J = 8.8 Hz), 8.15 (1H, dd, J_1 = 7.8 Hz, $J_{2=}$ 0.8 Hz), 7.82 (1H, td, J_1 = 7.7 Hz, $J_{2=}$ 1.7 Hz), 7.43-7.39 (1H, m), 7.27-7.23 (4H, m), 7.18-7.15 (2H, m), 7.10-7.09 (5H, m), 6.97 (2H, d, J = 7.6 Hz), 4.70-4.68 (1H, m), 4.25-4.14 (6H, m), 3.07-2.96 (2H, m), 2.08 (3H, s).

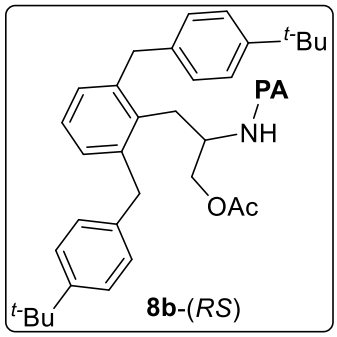
$^{13}C\{^1H\}$ NMR (~101 MHz, $CDCl_3$): δ_C 170.8, 163.8, 149.5, 148.0, 140.8, 140.0, 137.3, 134.4, 129.3, 128.7, 128.4, 127.0, 126.2, 126.0, 122.2, 65.1, 49.1, 39.1, 31.2, 20.9.

HRMS (ESI): *m/z* $(M + H)^+$ calcd for $C_{31}H_{31}N_2O_3$: 479.2335 found: 479.2331.

$(\alpha)^{25}_D$ = -48.7 (c = 0.03 g/mL, $CHCl_3$).

The enantiomeric ratio (*er* 96:4) of compound **8a**-(S) was determined by using the Daicel Chiralpak IA column, hexane/*i*-PrOH 90:10, flow rate 1.0 mL/min, UV detection at 254 nm, t_R = 12.76 min, t_S = 14.75 min.

3-(2,6-Bis(4-(*tert*-butyl)benzyl)phenyl)-2-(picolinamido)propyl acetate (8b-(RS)):



Compound **8b**-(RS) was obtained from procedure D after purification by column chromatography on silica gel (EtOAc:hexanes = 40:60) as a colourless solid (78 mg, 66%, 0.20 mmol scale). R_f (EtOAc/hexanes = 40:60) 0.7. mp: 98-100 ºC.

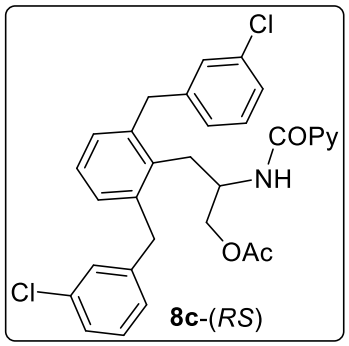
IR (DCM): 3375, 1740, 1515 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ_H 8.60 (1H, d, J = 4.3 Hz), 8.33 (1H, d, J = 7.3 Hz), 8.20 (1H, d, J = 7.6 Hz), 7.87 (1H, td, J_1 = 7.7 Hz, $J_{2=}$ 0.8 Hz), 7.47-7.44 (1H, m), 7.33-7.28 (4H, m), 7.16-7.01 (7H, m), 4.77-4.73 (1H, m), 4.26-4.16 (6H, m), 3.13-3.03 (2H, m), 2.13 (3H, s), 1.34 (18H, s).

$^{13}C\{^1H\}$ NMR (~101 MHz, $CDCl_3$): δ_C 170.8, 163.7, 149.6, 148.7, 148.0, 140.1, 137.7, 137.3, 134.3, 129.2, 128.3, 126.9, 126.2, 125.2, 122.3, 65.0, 49.2, 38.5, 34.3, 31.3, 31.2, 20.9.

HRMS (ESI): *m/z* $(M + H)^+$ calcd for $C_{39}H_{47}N_2O_3$: 591.3587 found: 591.3588.

3-(2,6-Bis(3-chlorobenzyl)phenyl)-2-(picolinamido)propyl acetate (8c-(RS)):



Compound **8c**-(RS) was obtained from procedure D after purification by column chromatography on silica gel (EtOAc:hexanes = 40:60) as a colourless solid (69 mg, 63%, 0.20 mmol scale). R_f (EtOAc/hexanes = 40:60) 0.6. mp: 126-128 ºC.

IR (DCM): 3330, 1739, 1518 cm^{-1}.

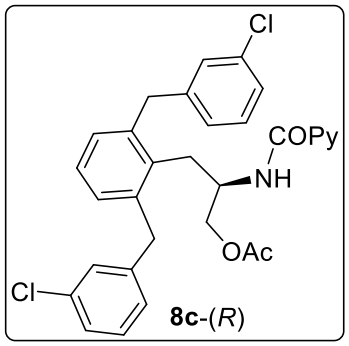
^1H NMR (400 MHz, $CDCl_3$): δ_H 8.57-8.55 (1H, m), 8.28 (1H, d, J = 9.1 Hz), 8.15 (1H, dt, J_1 = 1.9 Hz, J_2 = 1.0 Hz), 7.84 (1H, td, J_1 = 7.7 Hz, J_2 = 1.7 Hz), 7.45-7.41 (1H, m), 7.20-7.11 (5H, m), 7.06 (2H, br. s), 6.98-6.95 (4H, m), 4.68-4.62 (1H, m), 4.24-4.11 (6H, m), 2.99-2.88 (2H, m), 2.11 (3H, s).

$^{13}C\{^1H\}$ NMR (~101 MHz, $CDCl_3$): δ_C 170.9, 163.9, 149.4, 148.2, 142.9, 139.3, 137.4, 134.4, 134.3, 129.7, 128.8, 127.4, 126.9, 126.4, 126.3, 122.3, 65.1, 49.2, 38.8, 31.4, 21.0.

HRMS (ESI): *m/z* $(M + H)^+$ calcd for $C_{31}H_{29}Cl_2N_2O_3$: 547.1555 found: 547.1562.

The HPLC of compound **8c**-(RS) was determined by using the Daicel Chiracel OD-H column, hexane/*i*-PrOH 95:05, flow rate 1.0 mL/min, UV detection at 254 nm, t_R = 31.71 min, t_S = 28.30 min.

(R)-3-(2,6-Bis(3-chlorobenzyl)phenyl)-2-(picolinamido)propyl acetate (8c-(R)):



Compound **8c**-(R) was obtained from procedure D after purification by column chromatography on silica gel (EtOAc:hexanes = 40:60) as a colourless solid (70 mg, 64%, 0.20 mmol scale). R_f (EtOAc/hexanes = 40:60) 0.6. mp: 127-129 ºC.

IR (DCM): 3322, 1741, 1519 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ_H 8.56-8.55 (1H, m), 8.28 (1H, d, J = 9.1 Hz), 8.15 (1H, d, J = 7.8 Hz), 7.84 (1H, td, J_1 = 7.6 Hz, J_2 = 1.7 Hz), 7.44-7.41 (1H, m), 7.19-7.11 (5H, m), 7.06 (2H, br. s), 6.98-6.95 (4H, m), 4.68-4.62 (1H, m), 4.24-4.12 (6H, m), 2.99-2.88 (2H, m), 2.11 (3H s).

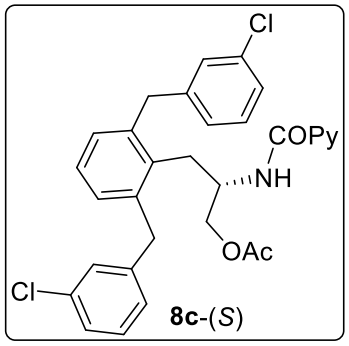
$^{13}C\{^1H\}$ NMR (~101 MHz, $CDCl_3$): δ_C 170.8, 163.8, 149.3, 148.1, 142.8, 139.3, 137.3, 134.4, 134.2, 129.6, 128.7, 127.3, 127.0, 126.3, 126.2, 122.2, 65.0, 49.1, 38.7, 31.3, 20.9.

HRMS (ESI): *m/z* $(M + Na)^+$ calcd for $C_{31}H_{28}Cl_2N_2NaO_3$: 569.1375 found: 569.1377.

$(\alpha)^{25}_D$ = 29.9 (c = 0.02 g/mL, $CHCl_3$).

The enantiomeric ratio (*er* 97:3) of compound **8c**-(R) was determined by using the Daicel Chiralcel OD-H column, hexane/*i*-PrOH 90:05, flow rate 1.0 mL/min, UV detection at 254 nm, t_R = 31.67 min, t_S = 29.02 min.

(S)-3-(2,6-Bis(3-chlorobenzyl)phenyl)-2-(picolinamido)propyl acetate (8c-(S)):



Compound **8c**-(S) was obtained from procedure D after purification by column chromatography on silica gel (EtOAc:hexanes = 40:60) as a colourless solid (71 mg, 65%, 0.20 mmol scale). R_f (EtOAc/hexanes = 40:60) 0.6. mp: 126-128 ºC.

IR (DCM): 3366, 1740, 1518 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ_H 8.56-8.55 (1H, m), 8.28 (1H, d, J = 9.2 Hz), 8.15 (1H, d, J = 7.8 Hz), 7.83 (1H, td, J_1 = 7.6 Hz, J_2 = 1.7 Hz), 7.45-7.41 (1H, m), 7.20-7.11 (5H, m), 7.06 (2H, br. s), 6.98-6.95 (4H, m), 4.68-4.62 (1H, m), 4.24-4.11 (6H, m), 2.99-2.88 (2H, m), 2.11 (3H, s).

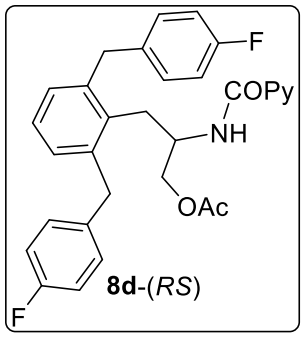
$^{13}C\{^1H\}$ NMR (~101 MHz, $CDCl_3$): δ_C 170.9, 163.9, 149.4, 148.1, 142.9, 139.3, 137.4, 134.4, 134.3, 129.7, 128.8, 127.4, 126.9, 126.4, 126.3, 122.3, 65.1, 49.2, 38.8, 31.4, 21.0.

HRMS (ESI): *m/z* $(M + H)^+$ calcd for $C_{31}H_{29}Cl_2N_2O_3$: 547.1555 found: 547.1542.

$(\alpha)^{25}_D$ = -39.9 (c = 0.02 g/mL, $CHCl_3$).

The enantiomeric ratio (*er* 98:2) of compound **8c**-(S) was determined by using the Daicel Chiralcel OD-H column, hexane/*i*-PrOH 95:05, flow rate 1.0 mL/min, UV detection at 254 nm, t_R = 32.93 min, t_S = 28.32 min.

3-(2,6-Bis(4-fluorobenzyl)phenyl)-2-(picolinamido)propyl acetate (8d-(RS)):



Compound **8d**-(RS) was obtained from procedure D after purification by column chromatography on silica gel (EtOAc:hexanes = 40:60) as a colourless solid (62 mg, 60%, 0.20 mmol scale). R_f (EtOAc/hexanes = 40:60) 0.65. mp: 120-122 ºC.

IR (DCM): 3367, 1739, 1511 cm^{-1}.

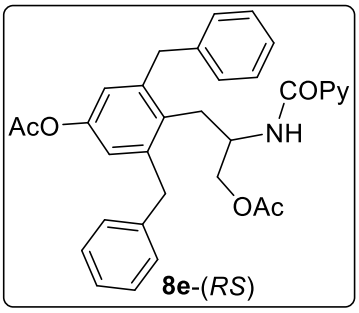
^1H NMR (400 MHz, $CDCl_3$): δ_H 8.55-8.54 (1H, m), 8.28 (1H, d, J = 9.1 Hz), 8.15 (1H, dt, J_1 = 1.8 Hz, J_2 = 1.0 Hz), 7.84 (1H, td, J_1 = 7.6 Hz, J_2 = 1.7 Hz), 7.45-7.41 (1H, m), 7.13-7.02 (5H, m), 6.96-6.90 (6H, m), 4.70-4.62 (1H, m), 4.22-4.10 (6H, m), 3.04-2.92 (2H, m), 2.09 (3H, s).

$^{13}C\{^1H\}$ NMR (~101 MHz, $CDCl_3$): δ_C 170.9, 163.9, 161.4 (d, J_{C-F} = 242.6 Hz), 149.5, 148.1, 140.0, 137.4, 136.4 (d, J_{C-F} = 3.3 Hz), 134.2, 130.1 (d, J_{C-F}= 7.7 Hz), 129.4, 127.2, 126.4, 122.3, 115.2 (d, J_{C-F} = 21.0 Hz), 65.1, 49.2, 38.3, 31.2, 21.0.

$^{19}F\{^1H\}$ NMR (~376 MHz, $CDCl_3$): δ_F = -117.24.

HRMS (ESI): *m/z* $(M + H)^+$ calcd for $C_{31}H_{29}F_2N_2O_3$: 515.2146 found: 515.2161.

3-(4-Acetoxy-2,6-dibenzylphenyl)-2-(picolinamido)propyl acetate (8e-(RS)):



Compound **8e**-(RS) was obtained from procedure D after purification by column chromatography on silica gel (EtOAc:hexanes = 50:50) as a colourless solid (40 mg, 75%, 0.1 mmol scale). R_f (EtOAc/hexanes = 50:50) 0.6. mp: 90-92 ^{o}C;

IR (DCM): 3378, 1740, 1515 cm^{-1}.

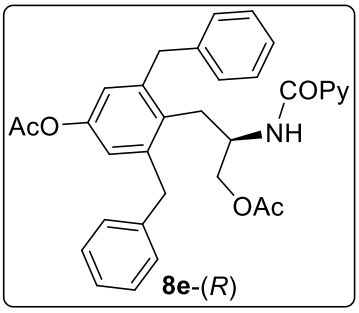
^{1}H NMR (400 MHz, $CDCl_3$): δ_H 8.55-8.54 (1H, m), 8.29 (1H, d, J = 9.0 Hz), 8.16 (1H, d, J = 7.8 Hz), 7.84 (1H, td, J_1 = 7.7 Hz, J_2 = 1.7 Hz), 7.44-7.41 (1H, m), 7.26-7.24 (4H, m), 7.20-7.17 (2H, m), 7.11 (4H, d, J = 7.3 Hz), 6.70 (2H, s), 4.69-4.65 (1H, m), 4.23-4.13 (6H, m), 3.07-2.95 (2H, m), 2.18 (3H, s), 2.09 (3H, s).

^{13}C{^{1}H} NMR (~101 MHz, $CDCl_3$): δ_C 170.8, 169.3, 163.8, 149.4, 149.3, 148.0, 141.6, 140.0, 137.4, 131.9, 128.8, 128.5, 126.3, 126.1, 122.3, 121.9, 65.0, 49.0, 39.0, 30.8, 21.1, 20.9.

HRMS (ESI): *m/z* $(M + H)^+$ calcd for $C_{33}H_{33}N_2O_5$: 537.2389; found: 537.2391.

The HPLC of compound **8e**-(RS) was determined by using the Daicel Chiralpak IA column, hexane/*i*-PrOH 95:05, flow rate 1.0 mL/min, UV detection at 254 nm, t_R = 35.11 min, t_S = 42.38 min.

(R)-3-(4-Acetoxy-2,6-dibenzylphenyl)-2-(picolinamido)propyl acetate (8e-(R)):



Compound **8e**-(R) was obtained from procedure D after purification by column chromatography on silica gel (EtOAc:hexanes = 50:50) as a colourless solid (41 mg, 76%, 0.1 mmol scale). R_f (EtOAc/hexanes = 50:50) 0.6. mp: 91-93 ^{o}C.

IR (DCM): 3369, 1740, 1515 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ_H 8.57 (1H, d, J = 4.2 Hz), 8.32 (1H, d, J = 9.1 Hz), 8.19 (1H, d, J = 7.8 Hz), 7.86 (1H, td, J_1 = 7.7 Hz, J_2 = 1.6 Hz), 7.47-7.44 (1H, m), 7.31-7.28 (4H, m), 7.23-7.20 (2H, m), 7.14 (4H, d, J = 7.2 Hz), 6.73 (2H, s), 4.73-4.67 (1H, m), 4.27-4.16 (6H, m), 3.10-2.98 (2H, m), 2.21 (3H, s), 2.12 (3H, s).

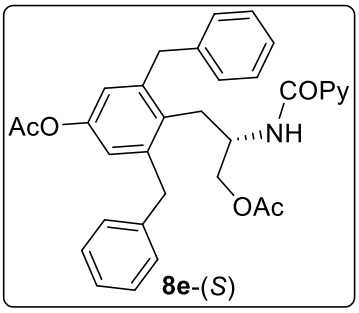
^{13}C {^{1}H} NMR (~101 MHz, $CDCl_3$): δ_C 170.9, 169.3, 163.9, 149.5, 149.4, 148.1, 141.6, 140.1, 137.4, 131.9, 128.9, 128.6, 126.3, 126.2, 122.4, 122.0, 65.1, 49.1, 39.1, 30.9, 21.1, 20.9.

HRMS (ESI): *m/z* $(M + H)^+$ calcd for $C_{33}H_{33}N_2O_5$: 537.2389; found: 537.2394.

$(\alpha)^{25}_D$ = 45.9 (c = 0.02 g/mL, $CHCl_3$).

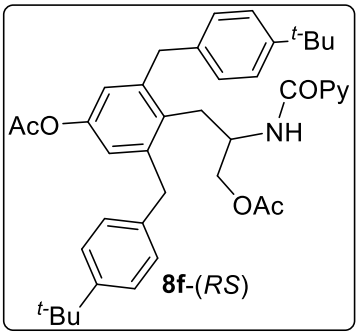
The enantiomeric ratio (*er* 97:3) of compound **8e**-(R) was determined by using the Daicel Chiralpak IA column, hexane/*i*-PrOH 95:05, flow rate 1.0 mL/min, UV detection at 254 nm, t_R = 34.68 min, t_S = 42.21 min.

(S)-3-(4-Acetoxy-2,6-dibenzylphenyl)-2-(picolinamido)propyl acetate (8e-(S)):



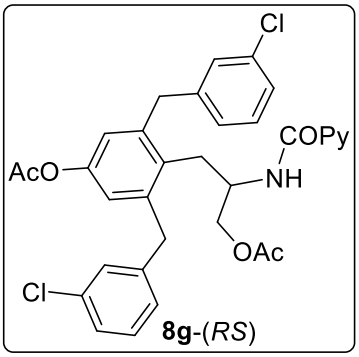
Compound **8e**-(S) was obtained from procedure D after purification by column chromatography on silica gel (EtOAc:hexanes = 50:50) as a colourless solid (38 mg, 71%, 0.1 mmol scale). R_f (EtOAc/hexanes = 50:50) 0.6. mp: 90-92 ºC;
IR (DCM): 3376, 1741, 1515 cm^{-1}.
^1H NMR (400 MHz, $CDCl_3$): δ_H 8.55 (1H, d, J = 4.3 Hz), 8.29 (1H, d, J = 9.1 Hz), 8.16 (1H, d, J = 7.8 Hz), 7.84 (1H, td, J_1 = 7.7 Hz, J_2 = 1.7 Hz), 7.45-7.44 (1H, m), 7.28-7.20 (4H, m), 7.20-7.17 (2H, m), 7.11 (4H, d, J = 7.2 Hz), 6.69 (2H, s), 4.70-4.64 (1H, m), 4.23-4.13 (6H, m), 3.07-2.95 (2H, m), 2.18 (3H, s), 2.09 (3H, s).
$^{13}C\{^1H\}$ NMR (~101 MHz, $CDCl_3$): δ_C 170.9, 169.3, 163.9, 149.5, 149.4, 148.1, 141.6, 140.1, 137.4, 131.9, 128.9, 128.6, 126.3, 126.2, 122.4, 122.0, 65.1, 49.1, 39.1, 30.9, 21.1, 20.9.
HRMS (ESI): *m/z* $(M + H)^+$ calcd for $C_{33}H_{33}N_2O_5$: 537.2389; found: 537.2386.
$(\alpha)^{25}_D$ = -46.9 (c = 0.02 g/mL, $CHCl_3$).
The enantiomeric ratio (*er* 98:2) of compound **8e**-(S) was determined by using the Daicel Chiralpak IA column, hexane/*i*-PrOH 95:05, flow rate 1.0 mL/min, UV detection at 254 nm, t_R = 35.22 min, t_S = 41.90 min.

3-(4-Acetoxy-2,6-bis(4-(*tert*-butyl)benzyl)phenyl)-2-(picolinamido)propyl acetate (8f-(RS)):



Compound **8f**-(RS) was obtained from procedure D after purification by column chromatography on silica gel (EtOAc:hexanes = 50:50) as a colourless solid (42 mg, 65%, 0.1 mmol scale). R_f (EtOAc/hexanes = 50:50) 0.7. mp: 112-114 ºC.
IR (DCM): 3382, 1744, 1514 cm^{-1}.
^1H NMR (400 MHz, $CDCl_3$): δ_H 8.59-8.58 (1H, m), 8.32 (1H, d, J = 9.0 Hz), 8.19 (1H, d, J = 7.8 Hz), 7.87 (1H, td, J_1 = 7.7 Hz, J_2 = 1.7 Hz), 7.47-7.44 (1H, m), 7.31 (4H, d, J = 8.3 Hz), 7.06 (4H, d, J = 8.3 Hz), 6.75 (2H, s), 4.73-4.67(1H, m), 4.23-4.13 (6H, m), 3.11-3.00 (2H, m), 2.22 (3H, s), 2.12 (3H, s), 1.32 (18H, s).
$^{13}C\{^1H\}$ NMR (~101 MHz, $CDCl_3$): δ_C 170.9, 169.4, 163.9, 149.6, 149.3, 148.9, 148.1, 141.8, 137.4, 137.0, 131.9, 128.5, 126.3, 125.4, 122.4, 122.0, 65.0, 49.2, 38.5, 34.4, 31.4. 30.9, 21.2, 21.0.
HRMS (ESI): *m/z* $(M + H)^+$ calcd for $C_{41}H_{49}N_2O_5$: 649.3641; found: 649.3646.

3-(4-Acetoxy-2,6-bis(3-chlorobenzyl)phenyl)-2-(picolinamido)propyl acetate (8g-(RS)):



Compound **8g**-(RS) was obtained from procedure D after purification by column chromatography on silica gel (EtOAc:hexanes = 50:50) as a colourless semi solid (48 mg, 79%, 0.1 mmol scale). R_f (EtOAc/hexanes = 50:50) 0.6.

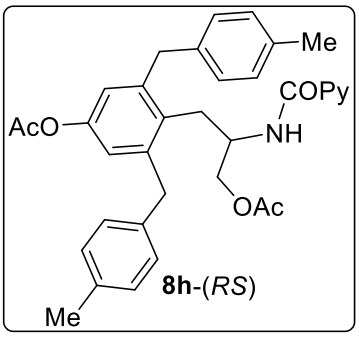
IR (DCM): 3380, 1742, 1517 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ_H 8.55 (1H, d, J = 4.7 Hz), 8.30 (1H, d, J = 9.1 Hz), 8.16 (1H, d, J = 7.8 Hz), 7.85 (1H, td, J_1 = 7.7 Hz, J_2 = 1.6 Hz), 7.46-7.42 (1H, m), 7.21-7.15 (4H, m), 7.09 (2H, s), 6.97 (2H, d, J = 6.9 Hz), 6.71 (2H, s), 4.67-4.59 (1H, m), 4.23-4.11 (6H, m), 3.00-2.88 (2H, m), 2.21 (3H, s), 2.21 (3H, s).

$^{13}C\{^1H\}$ NMR (~101 MHz, $CDCl_3$): δ_C 170.9, 169.3, 164.0, 149.5, 149.3, 148.2, 142.1, 141.0, 137.5, 134.4, 131.9, 129.9, 128.9, 127.0, 126.5, 126.4, 122.4, 122.3, 65.0, 49.1, 38.7, 31.0, 21.2, 21.0.

HRMS (ESI): *m/z* $(M + H)^+$ calcd for $C_{33}H_{31}Cl_2N_2O_5$: 605.1610; found: 605.1620.

3-(4-Acetoxy-2,6-bis(4-methylbenzyl)phenyl)-2-(picolinamido)propyl acetate (8h-(RS)):



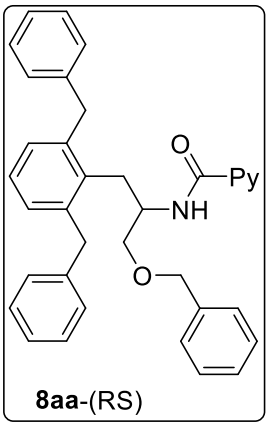
Compound **8h**-(RS) was obtained from procedure D after purification by column chromatography on silica gel (EtOAc:hexanes = 50:50) as a colourless solid (40 mg, 71%, 0.1 mmol scale. R_f (EtOAc/hexanes = 50:50) 0.65. mp: 146-148 ^oC; IR (DCM): 3381, 1742, 1513 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ_H 8.58-8.57 (1H, m), 8.32 (1H, d, J = 9.1 Hz), 8.18 (1H, d, J = 7.8 Hz), 7.86 (1H, td, J_1 = 7.7 Hz, J_2 = 1.7 Hz), 7.47-7.44 (1H, m), 7.10 (4H, d, J = 7.8 Hz), 7.02 (4H, d, J = 8.0 Hz), 6.71 (2H, s), 4.73-4.67 (1H, m), 4.21-4.11 (6H, m), 3.10-2.99 (2H, m), 2.33 (6H, s), 2.21 (3H, s), 2.12 (3H, s).

$^{13}C\{^1H\}$ NMR (~101 MHz, $CDCl_3$): δ_C 170.9, 169.4, 163.9, 149.5, 149.3, 148.1, 141.8, 137.4, 137.0, 135.7, 131.9, 129.2, 128.8, 126.3, 122.3, 121.9, 65.1, 49.1, 38.7, 30.8, 21.2, 21.0, 21.0.

HRMS (ESI): *m/z* $(M + H)^+$ calcd for $C_{35}H_{37}N_2O_5$: 565.2702; found: 565.2708.

***N*-(1-(Benzyloxy)-3-(2,6-dibenzylphenyl)propan-2-yl)picolinamide (8aa-(RS)):**



Compound **8aa**-(RS) was obtained from procedure D after purification by column chromatography on silica gel (EtOAc: hexanes = 30:70) as a colourless semi-solid (50 mg, 95%, 0.1 mmol scale); R_f (EtOAc/hexanes = 30:70) 0.3.

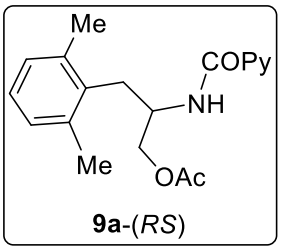
IR (DCM): 3398, 1674, 1592 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ_H 8.58-8.55 (2H, m), 8.16 (1H, d, J = 7.8 Hz), 7.81 (1H, td, J_1 = 7.7 Hz, J_2 = 1.7 Hz), 7.42-7.26 (6H, m), 7.24-7.19 (4H, m), 7.16-7.10 (3H, m), 7.06 (4H, d, J = 7.1 Hz), 6.98 (2H, d, J = 7.5 Hz), 4.61-4.51 (3H, m), 4.29-4.19 (4H, m), 3.56 (1H, dd, J_1 = 9.4 Hz, J_2 = 2.6 Hz), 3.51 (1H, dd, J_1 = 9.4 Hz, J_2 = 3.8 Hz), 3.11 (1H, dd, J_1 = 14.0 Hz, J_2 = 9.4 Hz), 3.00 (1H, dd, J_1 = 14.1 Hz, J_2 = 5.9 Hz).

^{13}C {^1H} NMR (~101 MHz, $CDCl_3$): δ_C 163.7, 150.0, 148.1, 141.3, 140.4, 137.9, 137.3, 135.3, 129.2, 128.8, 128.4, 128.3, 127.9, 127.8, 126.7, 126.1, 125.8, 122.2, 73.3, 69.9, 50.1, 38.8, 31.2.

HRMS (ESI): *m/z* $(M + H)^+$ calcd for $C_{36}H_{35}N_2O_2$: 527.2699; found: 527.2697.

3-(2,6-Dimethylphenyl)-2-(picolinamido)propyl acetate (9a-(RS)):



Compound **9a**-(RS) was obtained from procedure E after purification by column chromatography on silica gel (EtOAc:hexanes = 40:60) as a colourless solid (46 mg, 70%, 0.20 mmol scale). R_f (EtOAc/hexanes = 40:60) 0.55. mp: 122-124 ºC.

IR (DCM): 3371, 1739, 1519 cm^{-1}.

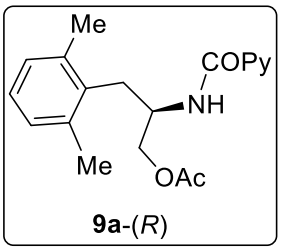
^1H NMR (400 MHz, $CDCl_3$): δ_H 8.58 (1H, d, J = 4.6 Hz), 8.31 (1H, d, J = 9.0 Hz), 8.16 (1H, d, J = 7.8 Hz), 7.84 (1H, td, J_1 = 7.7 Hz, J_2 = 1.6 Hz), 7.45-7.42 (1H, m), 7.04-6.98 (3H, m), 4.67-4.61 (1H, m), 4.19-4.12 (2H, m), 3.11-3.01 (2H, m), 2.43 (6H, s), 2.10 (3H, s).

^{13}C{^1H} NMR (~101 MHz, $CDCl_3$): δ_C 171.0, 163.9, 149.6, 148.1, 137.4, 137.0, 134.1, 128.5, 126.6, 126.3, 122.3, 65.1, 48.5, 31.9, 20.9, 20.3.

HRMS (ESI): *m/z* $(M + Na)^+$ calcd for $C_{19}H_{22}N_2NaO_3$: 349.1528 found: 349.1536.

The HPLC of compound **9a**-(RS) was determined by using the Daicel Chiralcel OJ column, hexane/*i*-PrOH 90:10, flow rate 1.0 mL/min, UV detection at 254 nm, t_R = 22.05 min, t_S = 18.73 min.

(R)-3-(2,6-Dimethylphenyl)-2-(picolinamido)propyl acetate (9a-(R)):



9a-(*R*)

Compound **9a**-(R) was obtained from procedure E after purification by column chromatography on silica gel (EtOAc:hexanes = 40:60) as a colourless solid (48 mg, 74%, 0.20 mmol scale). R_f (EtOAc/hexanes = 40:60) 0.55. mp: 122-124 ºC.

IR (DCM): 3381, 1738, 1518 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ_H 8.58 (1H, d, J = 4.6 Hz), 8.31 (1H, d, J = 8.7 Hz), 8.17 (1H, d, J = 7.8 Hz), 7.85 (1H, t, J = 7.7 Hz), 7.46-7.43 (1H, m), 7.04-6.98 (3H, m), 4.68-4.62 (1H, m), 4.19-4.12 (2H, m), 3.11-3.01 (2H, m), 2.43 (6H, s), 2.10 (3H, s).

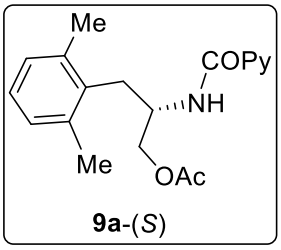
$^{13}C\{^1H\}$ NMR (~101 MHz, $CDCl_3$): δ_C 171.0, 163.8, 149.5, 148.0, 137.5, 137.0, 134.1, 128.5, 126.6, 126.3, 122.4, 65.1, 48.5, 31.8, 20.9, 20.3.

HRMS (ESI): *m/z* $(M + H)^+$ calcd for $C_{19}H_{23}N_2O_3$: 327.1709 found: 327.1718.

$(\alpha)^{25}_D$ = 62.0 (c = 0.02 g/mL, $CHCl_3$).

The enantiomeric ratio (*er* 98:2) of compound **9a**-(R) was determined by using the Daicel Chiralcel OJ column, hexane/*i*-PrOH 90:10, flow rate 1.0 mL/min, UV detection at 254 nm, t_R = 21.91 min, t_S = 19.00 min.

(S)-3-(2,6-Dimethylphenyl)-2-(picolinamido)propyl acetate (9a-(S)):



9a-(*S*)

Compound **9a**-(S) was obtained from procedure E after purification by column chromatography on silica gel (EtOAc:hexanes = 40:60) as a colourless solid (50 mg, 76%, 0.20 mmol scale). R_f (EtOAc/hexanes = 40:60) 0.55. mp: 123-125 ºC.

IR (DCM): 3368, 1739, 1519 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ_H 8.59-8.57 (1H, m), 8.35 (1H, d, J = 8.9 Hz), 8.17 (1H, d, J = 7.8 Hz), 7.86 (1H, td, J_1 = 7.7 Hz, J_2 = 1.7 Hz), 7.47-7.43 (1H, m), 7.04-6.98 (3H, m), 4.68-4.61 (1H, m), 4.19-4.12 (2H, m), 3.11-3.01 (2H, m), 2.43 (6H, s), 2.10 (3H, s).

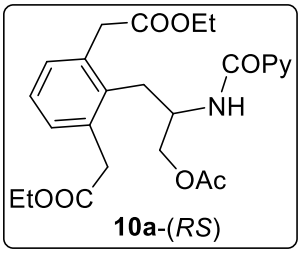
$^{13}C\{^1H\}$ NMR (~101 MHz, $CDCl_3$): δ_C 171.0, 163.7, 149.5, 147.9, 137.6, 137.0, 134.1, 128.5, 126.6, 126.3, 122.4, 65.1, 48.5, 31.8, 20.9, 20.3.

HRMS (ESI): *m/z* $(M + H)^+$ calcd for $C_{19}H_{23}N_2O_3$: 327.1709 found: 327.1708.

$(\alpha)^{25}_D$ = -63.0 (c = 0.02 g/mL, $CHCl_3$).

The enantiomeric ratio (*er* 99:1) of compound **9a**-(S) was determined by using the Daicel Chiralcel OJ column, hexane/*i*-PrOH 90:10, flow rate 1.0 mL/min, UV detection at 254 nm, t_R = 22.58 min, t_S = 18.51 min.

Diethyl 2,2'-(2-(3-acetoxy-2-(picolinamido)propyl)-1,3-phenylene)diacetate (10a-(RS)):



Compound **10a**-(RS) was obtained from procedure E after purification by column chromatography on silica gel (EtOAc:hexanes = 40:60) as a colourless solid (30 mg, 64%, 0.10 mmol scale). R_f (EtOAc/hexanes = 40:60) 0.3. mp: 58-60 ºC.

IR (DCM): 3343, 1735, 1520 cm^{-1}.

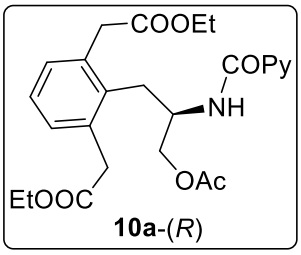
^1H NMR (400 MHz, $CDCl_3$): δ_H 8.59-8.57 (1H, m), 8.36 (1H, d, J = 8.8 Hz), 8.16 (1H, dt, J_1 = 1.9 Hz, J_2 = 0.9 Hz), 7.85 (1H, td, J_1 = 7.7 Hz, J_2 = 1.7 Hz), 7.46-7.43 (1H, m), 7.17 (3H, s), 4.63-4.57 (1H, m), 4.21-4.08 (6H, m), 3.89-3.81 (4H, m), 3.21 (1H, dd, J_1 = 14.6 Hz, J_2 = 6.2 Hz), 3.10 (1H, dd, J_1 = 14.7 Hz, J_2 = 9.4 Hz), 2.15 (3H, s), 1.23 (6H, t, J = 7.2 Hz).

$^{13}C\{^1H\}$ NMR (~101 MHz, $CDCl_3$): δ_C 171.7, 170.9, 164.0, 149.5, 148.2, 137.4, 134.7, 134.3, 130.0, 127.2, 126.3, 122.3, 64.5, 61.0, 49.2, 39.0, 31.2, 20.9, 14.1.

HRMS (ESI): *m/z* $(M + H)^+$ calcd for $C_{25}H_{31}N_2O_7$: 471.2131 found: 471.2144.

The HPLC of compound **10a**-(RS) was determined by using the Daicel Chiralpak IC column, hexane/*i*-PrOH 50:50, flow rate 1.0 mL/min, UV detection at 254 nm, t_R = 21.33 min, t_S = 17.54 min.

(R)-Diethyl 2,2'-(2-(3-acetoxy-2-(picolinamido)propyl)-1,3-phenylene)diacetate (10a-(R)):



Compound **10a**-(R) was obtained from procedure E after purification by column chromatography on silica gel (EtOAc:hexanes = 40:60) as a colourless solid (59 mg, 63%, 0.20 mmol scale). R_f (EtOAc/hexanes = 40:60) 0.3. mp: 59-61 ºC.

IR (DCM): 3357, 1735, 1520 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ_H 8.58 (1H, d, J = 4.6 Hz), 8.35 (1H, d, J = 8.8 Hz), 8.16 (1H, d, J = 7.8 Hz), 7.85 (1H, td, J_1 = 7.7 Hz, J_2 = 1.7 Hz), 7.46-7.43 (1H, m), 7.17 (3H, s), 4.63-4.57 (1H, m), 4.20-4.08 (6H, m), 3.89-3.81 (4H, m), 3.21 (1H, dd, J_1 = 14.6 Hz, $J_{2=}$ 6.2 Hz), 3.10 (1H, dd, J_1 = 14.6 Hz, $J_{2=}$ 9.4 Hz), 2.15 (3H, s), 1.23 (6H, t, J = 7.2 Hz).

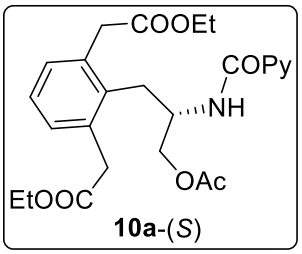
$^{13}C\{^1H\}$ NMR (~101 MHz, $CDCl_3$): δ_C 171.7, 170.9, 164.0, 149.5, 148.1, 137.4, 134.7, 134.3, 130.0, 127.2, 126.3, 122.3, 64.5, 61.0, 49.2, 39.0, 31.2, 20.9, 14.1.

HRMS (ESI): *m/z* $(M + H)^+$ calcd for $C_{25}H_{31}N_2O_7$: 471.2131 found: 471.2141.

$(\alpha)^{25}_D$ = 67.0 (c = 0.02 g/mL, $CHCl_3$).

The enantiomeric ratio (*er* 99:1) of compound **10a**-(R) was determined by using the Daicel Chiralpak IC column, hexane/*i*-PrOH 50:50, flow rate 1.0 mL/min, UV detection at 254 nm, t_R = 20.98 min, t_S = 17.57 min.

(S)-Diethyl 2,2'-(2-(3-acetoxy-2-(picolinamido)propyl)-1,3-phenylene)diacetate (10a-(S)):



Compound **10a**-(S) was obtained from procedure E after purification by column chromatography on silica gel (EtOAc:hexanes = 40:60) as a colourless solid (58 mg, 62%, 0.20 mmol scale). R_f (EtOAc/hexanes = 40:60) 0.3. mp: 60-62 ºC.

IR (DCM): 3367, 1735, 1521 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ_H 8.58 (1H, d, *J* = 4.3 Hz), 8.36 (1H, d, *J* = 8.8 Hz), 8.15 (1H, d, *J* = 7.8 Hz), 7.86-7.82 (1H, m), 7.45-7.42 (1H, m), 7.17 (3H, s), 4.63-4.58 (1H, m), 4.21-4.08 (6H, m), 3.90-3.82 (4H, m), 3.21 (1H, dd, J_1 = 14.6 Hz, J_2 = 6.2 Hz), 3.11 (1H, dd, J_1 = 14.6 Hz, J_2 = 9.4 Hz), 2.15 (3H, s), 1.23 (6H, t, *J* = 7.2 Hz).

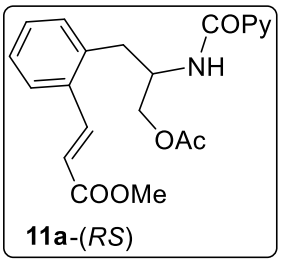
^{13}C{^{1}H} NMR (~101 MHz, $CDCl_3$): δ_C 171.6, 170.8, 163.9, 149.4, 148.0, 137.3, 134.6, 134.2, 129.9, 127.1, 126.2, 122.2, 64.4, 60.8, 49.1, 38.9, 31.1, 20.8, 14.0.

HRMS (ESI): *m/z* $(M + H)^+$ calcd for $C_{25}H_{31}N_2O_7$: 471.2131 found: 471.2121.

$(\alpha)^{25}_D$ = -49.0 (*c* = 0.02 g/mL, $CHCl_3$).

The enantiomeric ratio (*er* 97:3) of compound **10a**-(S) was determined by using the Daicel Chiralpak IC column, hexane/*i*-PrOH 50:50, flow rate 1.0 mL/min, UV detection at 254 nm, t_R = 21.23 min, t_S = 17.26 min.

Methyl (*E*)-3-(2-(3-acetoxy-2-(picolinamido)propyl)phenyl)acrylate (11a-(RS)):



Compound **11a**-(RS) was obtained from procedure F after purification by column chromatography on silica gel (EtOAc:hexanes = 40:60) as a colourless solid (19 mg, 20%, 0.25 mmol scale). R_f (EtOAc/hexanes = 40:60) 0.4. mp: 102-104 ºC.

IR (DCM): 3371, 1740, 1521 cm^{-1}.

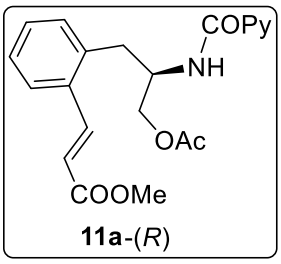
^{1}H NMR (400 MHz, $CDCl_3$): δ_H 8.55 (1H, d, *J* = 4.2 Hz), 8.27 (1H, d, *J* = 8.8 Hz), 8.17-8.16 (2H, m), 7.84 (1H, td, J_1 = 7.7 Hz, J_2 = 1.6 Hz), 7.57 (1H, d, *J* = 7.6 Hz), 7.45-7.42 (1H, m), 7.32 (2H, d, *J* = 3.9 Hz), 7.28-7.24 (1H, m), 6.35 (1H, d, *J* = 15.7 Hz), 4.62-4.55 (1H, m), 4.15 (1H, dd, J_1 = 11.4 Hz, J_2 = 4.3 Hz), 4.09 (1H, dd, J_1 = 11.4 Hz, J_2 = 4.6 Hz), 3.79 (3H, s), 3.23-3.12 (2H, m), 2.15 (3H, s).

$^{13}C\{^{1}H\}$ NMR (~101 MHz, $CDCl_3$): δ_C 170.9, 167.0, 163.8, 149.3, 148.0, 141.7, 137.2, 136.8, 133.7, 130.8, 130.1, 127.3, 126.8, 126.2, 122.2, 119.8, 64.4, 51.6, 49.6, 34.3, 20.7.

HRMS (ESI): *m/z* $(M + H)^+$ calcd for $C_{21}H_{23}N_2O_5$: 383.1607 found: 383.1607.

The HPLC of compound **11a**-(RS) was determined by using the Daicel Chiralpak IC column, hexane/*i*-PrOH 50:50, flow rate 1.0 mL/min, UV detection at 254 nm, t_R = 17.40 min, t_S = 19.92 min.

(R)-Methyl (*E*)-3-(2-(3-acetoxy-2-(picolinamido)propyl)phenyl)acrylate (11a-(R)):



Compound **11a**-(R) was obtained from procedure F after purification by column chromatography on silica gel (EtOAc:hexanes = 40:60) as a colourless solid (19 mg, 20%, 0.25 mmol scale). R_f (EtOAc/hexanes = 40:60) 0.4. mp: 103-105 °C.

IR (DCM): 3387, 1740, 1525 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ_H 8.55-8.54 (1H, *m*), 8.27 (1H, d, *J* = 8.8 Hz), 8.17-8.12 (2H, m), 7.84 (1H, td, J_1 = 7.7 Hz, J_2 = 1.7 Hz), 7.57 (1H, d, *J* = 7.6 Hz), 7.45-7.41 (1H, m), 7.33-7.32 (2H, m), 7.27-7.23 (1H, m), 6.35 (1H, d, *J* = 15.7 Hz), 4.62-4.54 (1H, m), 4.15 (1H, dd, J_1 = 11.4 Hz, J_2 = 4.4 Hz), 4.09 (1H, dd, J_1 = 11.4 Hz, J_2 = 4.6 Hz), 3.79 (3H, s), 3.23-3.12 (2H, m), 2.15 (3H, s).

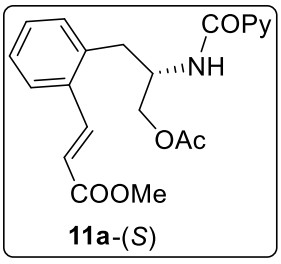
$^{13}C\{^{1}H\}$ NMR (~101 MHz, $CDCl_3$): δ_C 170.9, 167.1, 163.8, 149.3, 148.0, 141.7, 137.2, 136.8, 133.7, 130.8, 130.1, 127.3, 126.8, 126.2, 122.2, 119.8, 64.4, 51.6, 49.6, 34.3, 20.8.

HRMS (ESI): *m/z* $(M + H)^+$ calcd for $C_{21}H_{23}N_2O_5$: 383.1607 found: 383.1606.

$(\alpha)^{25}_D$ = 48.0 (*c* = 0.03 g/mL, $CHCl_3$).

The enantiomeric ratio (*er* 98:2) of compound **11a**-(R) was determined by using the Daicel Chiralpak IC column, hexane/*i*-PrOH 50:50, flow rate 1.0 mL/min, UV detection at 254 nm, t_R = 17.22 min, t_S = 20.03 min.

(S)-Methyl (*E*)-3-(2-(3-acetoxy-2-(picolinamido)propyl)phenyl)acrylate (11a-(S)):



Compound**, 11a**-(S) was obtained from procedure F after purification by column chromatography on silica gel (EtOAc:hexanes = 40:60) as a colourless solid (17 mg, 18%, 0.25 mmol scale). R_f (EtOAc/hexanes = 40:60) 0.4. mp: 102-104 °C.

IR (DCM): 3368, 1740, 1524 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ_H 8.58-8.56 (1H, m), 8.27 (1H, d, *J* = 8.8 Hz), 8.19-8.14 (2H, m), 7.86 (1H, td, J_1 = 7.7 Hz, J_2 = 1.6 Hz), 7.59 (1H, d, *J* = 7.6 Hz), 7.47-7.43 (1H, m), 7.35-

7.32 (2H, m), 7.30-7.25 (1H, m), 6.37 (1H, d, J = 15.8 Hz), 4.63-4.55 (1H, m), 4.17 (1H, dd, J_1 = 11.4 Hz, J_2 = 4.3 Hz), 4.10 (1H, dd, J_1 = 11.4 Hz, J_2 = 4.6 Hz), 3.81 (3H, s), 3.25-3.13 (2H, m), 2.17 (3H, s).

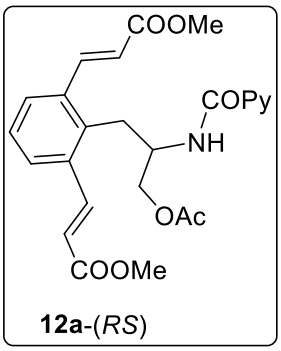
$^{13}C\{^1H\}$ NMR (~101 MHz, $CDCl_3$): δ_C 171.0, 167.2, 163.9, 149.4, 148.1, 141.8, 137.3, 136.9, 133.8, 131.0, 130.3, 127.4, 126.9, 126.3, 122.3, 119.9, 64.5, 51.7, 49.7, 34.4, 20.9.

HRMS (ESI): m/z $(M + H)^+$ calcd for $C_{21}H_{23}N_2O_5$: 383.1607 found: 383.1610.

$(\alpha)^{25}_D$ = -50.0 (c = 0.03 g/mL, $CHCl_3$).

The enantiomeric ratio (*er* 98:2) of compound **11a**-(S) was determined by using the Daicel Chiralpak IC column, hexane/*i*-PrOH 50:50, flow rate 1.0 mL/min, UV detection at 254 nm, t_R = 17.41 min, t_S = 19.74 min.

Dimethyl 3,3'-(2-(3-acetoxy-2-(picolinamido)propyl)-1,3-phenylene)(*2E,2'E*)-diacrylate (12a-(RS)):



12a-(*RS*)

Compound **12a**-(RS) was obtained from procedure F after purification by column chromatography on silica gel (EtOAc:hexanes = 40:60) as a colourless solid (44 mg, 38%, 0.25 mmol scale). R_f (EtOAc/hexanes = 40:60) 0.3. mp: 140-142 ^oC.

IR (DCM): 3365, 1720, 1519 cm^{-1}.

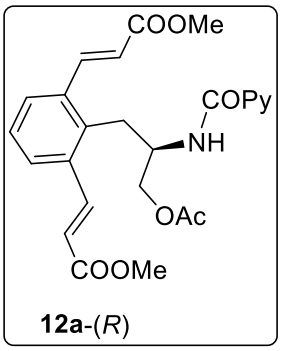
^1H NMR (400 MHz, $CDCl_3$): δ_H 8.54-8.53 (1H, m), 8.26-8.22 (3H, m), 8.13 (1H, d, J = 7.8 Hz), 7.83 (1H, td, J_1 = 7.7 Hz, J_2 = 1.7 Hz), 7.57 (2H, d, J = 7.8 Hz), 7.45-7.42 (1H, m), 7.31 (1H, d, J = 7.8 Hz), 6.32 (2H, d, J = 15.7 Hz), 4.54-4.46 (1H, m), 4.17 (1H, dd, J_1 = 11.4 Hz, J_2 = 4.8 Hz), 4.09 (1H, dd, J_1 = 11.3 Hz, J_2 = 3.9 Hz), 3.84 (6H, s), 3.35-3.32 (2H, m), 2.21 (3H, s).

$^{13}C\{^1H\}$ NMR (~101 MHz, $CDCl_3$): δ_C 171.0, 166.9, 163.9, 149.3, 148.0, 142.0, 137.3, 136.0, 135.4, 128.8, 127.7, 126.3, 122.3, 121.5, 64.6, 51.8, 49.7, 30.7, 20.8.

HRMS (ESI): m/z $(M + H)^+$ calcd for $C_{25}H_{27}N_2O_7$: 467.1818 found: 467.1830.

The HPLC of compound **12a**-(RS) was determined by using the Daicel Chiralpak IA column, hexane/*i*-PrOH 90:10, flow rate 1.0 mL/min, UV detection at 254 nm, t_R = 31.74 min, t_S = 36.11 min.

(R)-Dimethyl 3,3'-(2-((R)-3-acetoxy-2-(picolinamido)propyl)-1,3-phenylene)(*2E,2'E*)-diacrylate (12a-(R)):



Compound **12a**-(R) was obtained from procedure F after purification by column chromatography on silica gel (EtOAc:hexanes = 40:60) as a colourless solid (46 mg, 39%, 0.25 mmol scale). $_f$(EtOAc/hexanes = 40:60) 0.3. mp: 144-146 ^{o}C.

IR (DCM): 3364, 1718, 1518 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ_H 8.53-8.51 (1H, m), 8.26-8.20 (3H, m), 8.11 (1H, d, J = 7.8 Hz), 7.81 (1H, td, J_1 = 7.7 Hz, J_2 = 1.7 Hz), 7.55 (2H, d, J = 7.8 Hz), 7.44-7.40 (1H, m), 7.30-7.26 (1H, m), 6.31 (2H, d, J = 15.7 Hz), 4.52-4.46 (1H, m), 4.16 (1H, dd, J_1 = 11.3 Hz, J_2 = 4.8 Hz), 4.08 (1H, dd, J_1 = 11.4 Hz, J_2 = 3.9 Hz), 3.83 (6H, s), 3.37-3.27 (2H, m), 2.20 (3H, s).

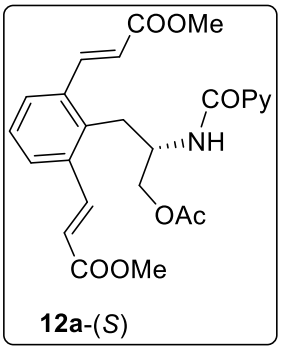
^{13}C{^{1}H} NMR (~101 MHz, $CDCl_3$): δ_C 171.0, 166.9, 163.9, 149.3, 148.0, 142.0, 137.3, 136.0, 135.4, 128.8, 127.7, 126.3, 122.3, 121.5, 64.6, 51.8, 49.7, 30.7, 20.8.

HRMS (ESI): *m/z* $(M + H)^+$ calcd for $C_{25}H_{27}N_2O_7$: 467.1818 found: 467.1798.

$(\alpha)^{25}_D$ = 111.2 (*c* = 0.02 g/mL, $CHCl_3$).

The enantiomeric ratio (*er* 98:2) of compound **12a**-(R) was determined by using the Daicel Chiralpak IA column, hexane/*i*-PrOH 90:10, flow rate 1.0 mL/min, UV detection at 254 nm, t_R = 30.70 min, t_S = 35.90 min.

(S)-Dimethyl 3,3'-(2-((S)-3-acetoxy-2-(picolinamido)propyl)-1,3-phenylene)(*2E,2'E*)-diacrylate (12a-(S)):



Compound **12a**-(S) was obtained from procedure F after purification by column chromatography on silica gel (EtOAc:hexanes = 40:60) as a colourless solid (47 mg, 40%, 0.25 mmol scale). R_f(EtOAc/hexanes = 40:60) 0.3. mp: 140-142 ^{o}C.

IR (DCM): 3375, 1718, 1518 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ_H 8.52 (1H, d, J = 4.3 Hz), 8.26-8.20 (3H, m), 8.11 (1H, d, J = 7.8 Hz), 7.81 (1H, td, J_1 = 7.7 Hz, J_2 = 1.7 Hz), 7.55 (2H, d, J = 7.8 Hz), 7.44-7.40 (1H, m), 7.30-7.26 (1H, m), 6.31 (2H, d, J = 15.7 Hz), 4.53-4.45 (1H, m), 4.16 (1H, dd, J_1 = 11.3 Hz, J_2 = 4.8 Hz), 4.09 (1H, dd, J_1 = 11.3 Hz, J_2 = 4.8 Hz), 3.83 (6H, s), 3.38-3.29 (2H, m), 2.20 (3H, s).

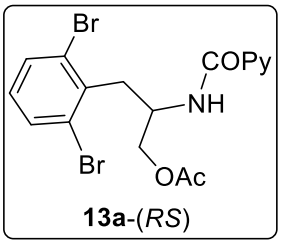
^{13}C{^{1}H} NMR (~101 MHz, $CDCl_3$): δ_C 170.9, 166.8, 163.7, 149.2, 147.9, 141.9, 137.1, 135.9, 135.3, 128.6, 127.6, 126.1, 122.1, 121.4, 64.5, 51.7, 49.6, 30.6, 20.7.

HRMS (ESI): *m/z* $(M + H)^+$ calcd for $C_{25}H_{27}N_2O_7$: 467.1818 found: 467.1821.

$(\alpha)^{25}_D$ = -112.1 (*c* = 0.02 g/mL, $CHCl_3$).

The enantiomeric ratio (*er* 98:2) of compound **12a**-(S) was determined by using the Daicel Chiralpak IA column, hexane/*i*-PrOH 90:10, flow rate 1.0 mL/min, UV detection at 254 nm, t_R = 30.40 min, t_S = 33.46 min.

3-(2,6-Dibromophenyl)-2-(picolinamido)propyl acetate (13a-(RS)):



13a-(*RS*)

Compound **13a**-(RS) was obtained from procedure G after purification by column chromatography on silica gel (EtOAc:hexanes = 40:60) as a colourless solid (29 mg, 46%, 0.136 mmol scale). R_f(EtOAc/hexanes = 40:60) 0.6. mp: 92-94 ºC.

IR (DCM): 3366, 1742, 1519 cm^{-1}.

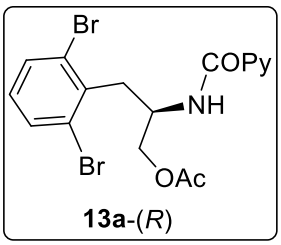
^1H NMR (400 MHz, $CDCl_3$): δ_H 8.59-8.57 (1H, m), 8.42 (1H, d, *J* = 9.3 Hz), 8.08 (1H, dt, J_1 = 7.8 Hz, J_2 = 1.0 Hz), 7.80 (1H, td, J_1 = 7.7 Hz, J_2 = 1.7 Hz), 7.47 (2H, d, *J* = 8.0 Hz), 7.43-7.40 (1H, m), 6.90 (1H, t, *J* = 8.0 Hz), 4.98-4.92 (1H, m), 4.35 (1H, dd, J_1 = 11.3 Hz, J_2 = 5.0 Hz), 4.24 (1H, dd, J_1 = 11.3 Hz, J_2 = 4.5 Hz), 3.46 (1H, dd, J_1 = 13.8 Hz, J_2 = 9.4 Hz), 3.35 (1H, dd, J_1 = 13.8 Hz, J_2 = 5.7 Hz), 2.12 (3H, s).

$^{13}C\{^1H\}$ NMR (~101 MHz, $CDCl_3$): δ_C 171.0, 164.0, 149.5, 148.1, 137.2, 136.6, 132.5, 129.4, 126.2, 126.0, 122.2, 65.8, 47.9, 38.3, 21.0.

HRMS (ESI): *m/z* $(M + H)^+$ calcd for $C_{17}H_{17}Br_2N_2O_3$: 454.9606 found: 454.9619.

The HPLC of compound **13a**-(RS) was determined by using the Daicel Chiralpak IC column, hexane/*i*-PrOH 50:50, flow rate 1.0 mL/min, UV detection at 254 nm, t_R = 13.47 min, t_S = 17.15 min.

(R)-3-(2,6-Dibromophenyl)-2-(picolinamido)propyl acetate (13a-(R)):



13a-(*R*)

Compound **13a**-(R) was obtained from procedure G after purification by column chromatography on silica gel (EtOAc:hexanes = 40:60) as a colourless solid (66 mg, 48%, 0.30 mmol scale). R_f(EtOAc/hexanes = 40:60) 0.6. mp: 94-96 ºC.

IR (DCM): 3368, 1742, 1519 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ_H 8.58 (1H, dd, J_1 = 4.7 Hz, J_2 = 0.6 Hz), 8.44 (1H, d, *J* = 9.3 Hz), 8.09 (1H, d, *J* = 7.8 Hz), 7.81 (1H, td, J_1 = 7.7 Hz, J_2 = 1.7 Hz), 7.47 (2H, d, *J* = 8.0 Hz), 7.43-7.40 (1H, m), 6.90 (1H, t, *J* = 8.0 Hz), 4.98-4.92 (1H, m), 4.35 (1H, dd, J_1 = 11.3 Hz, J_2 =

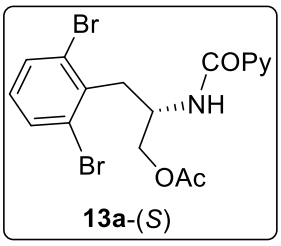
5.0 Hz), 4.24 (1H, dd, J_1 = 11.3 Hz, J_2 = 4.6 Hz), 3.46 (1H, dd, J_1 = 13.8 Hz, J_2 = 9.4 Hz), 3.36 (1H, dd, J_1 = 13.8 Hz, J_2 = 5.7 Hz), 2.11 (3H, s).

$^{13}C\{^1H\}$ NMR (~101 MHz, $CDCl_3$): δ_C 171.0, 164.0, 149.5, 148.1, 137.2, 136.6, 132.4, 129.4, 126.2, 126.0, 122.2, 65.8, 47.9, 38.3, 21.0.

HRMS (ESI): *m/z* $(M + H)^+$ calcd for $C_{17}H_{17}Br_2N_2O_3$: 454.9606 found: 454.9605.

$(\alpha)^{25}_D$ = 134.1 (*c* = 0.02 g/mL, $CHCl_3$). The enantiomeric ratio (*er* 99:1) of compound **13a**-(R) was determined by using the Daicel Chiralpak IC column, hexane/*i*-PrOH 50:50, flow rate 1.0 mL/min, UV detection at 254 nm, t_R = 12.89 min, t_S = 16.54 min.

(S)-3-(2,6-Dibromophenyl)-2-(picolinamido)propyl acetate (13a-(S)):



13a-(*S*)

Compound **13a**-(S) was obtained from procedure G after purification by column chromatography on silica gel (EtOAc:hexanes = 40:60) as a colourless solid (46 mg, 50%, 0.20 mmol scale). R_f (EtOAc/hexanes = 40:60) 0.6. mp: 94-96 °C.

IR (DCM): 3359, 1742 1519 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ_H 8.57 (1H, d, *J* = 4.7 Hz), 8.42 (1H, d, *J* = 9.3 Hz), 8.08 (1H, d, *J* = 7.8 Hz), 7.80 (1H, td, J_1 = 7.7 Hz, J_2 = 1.6 Hz), 7.47 (2H, d, *J* = 8.0 Hz), 7.43-7.40 (1H, m), 6.90 (1H, t, *J* = 8.0 Hz), 5.00-4.91 (1H, m), 4.35 (1H, dd, J_1 = 11.3 Hz, J_2 = 5.0 Hz), 4.24 (1H, dd, J_1 = 11.3 Hz, J_2 = 4.5 Hz), 3.46 (1H, dd, J_1 = 13.9 Hz, J_2 = 9.5 Hz), 3.35 (1H, dd, J_1 = 13.8 Hz, J_2 = 5.7 Hz), 2.12 (3H, s).

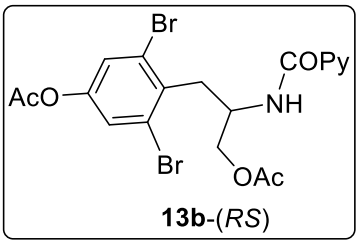
$^{13}C\{^1H\}$ NMR (~101 MHz, $CDCl_3$): δ_C 171.0, 164.0, 149.5, 148.1, 137.2, 136.6, 132.4, 129.4, 126.2, 126.0, 122.2, 65.8, 47.9, 38.3, 21.0.

HRMS (ESI): *m/z* $(M + H)^+$ calcd for $C_{17}H_{17}Br_2N_2O_3$: 454.9606 found: 454.9614.

$(\alpha)^{25}_D$ = -141.2 (*c* = 0.02 g/mL, $CHCl_3$).

The enantiomeric ratio (*er* 99:1) of compound **13a**-(S) was determined by using the Daicel Chiralpak IC column, hexane/*i*-PrOH 50:50, flow rate 1.0 mL/min, UV detection at 254 nm, t_R = 12.77 min, t_S = 16.23 min.

3-(4-Acetoxy-2,6-dibromophenyl)-2-(picolinamido)propyl acetate (13b-(RS)):



13b-(*RS*)

Compound **13b**-(RS) was obtained from procedure G after purification by column chromatography on silica gel (EtOAc:hexanes = 50:50) as a colourless solid (30 mg, 58%, 0.1 mmol scale). R_f (EtOAc/hexanes = 50:50) 0.55. mp: 101-103 °C.

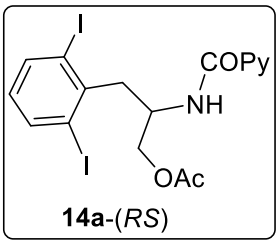
IR (DCM): 3362, 1767, 1517 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ_H 8.59-8.58 (1H, m), 8.42 (1H, d, J = 9.4 Hz), 8.11 (1H, d, J = 7.8 Hz), 7.83 (1H, td, J_1 = 7.7 Hz, J_2 = 1.7 Hz), 7.45-7.42 (1H, m), 7.32 (2H, s), 4.97-4.91 (1H, m), 4.36 (1H, dd, J_1 = 11.3 Hz, J_2 = 5.0 Hz), 4.25 (1H, dd, J_1 = 11.2 Hz, J_2 = 4.6 Hz), 3.45 (1H, dd, J_1 = 14.0 Hz, J_2 = 9.3 Hz), 3.34 (1H, dd, J_1 = 14.0 Hz, J_2 = 5.8 Hz), 2.27 (3H, s), 2.13 (3H, s).

^{13}C{^{1}H} NMR (~101 MHz, $CDCl_3$): δ_C 171.0, 168.5, 164.0, 149.4, 149.4, 148.1, 137.3, 134.2, 126.2, 125.8, 125.3, 122.3, 65.8, 47.8, 37.8, 21.0.

HRMS (ESI): *m/z* $(M + H)^+$ calcd for $C_{19}H_{19}Br_2N_2O_5$: 512.9661; found: 512.9650.

3-(2,6-Diiodophenyl)-2-(picolinamido)propyl acetate (14a-(RS)):



Compound **14a**-(RS) was obtained from procedure H after purification by column chromatography on silica gel (EtOAc:hexanes = 40:60) as a colourless solid (58 mg, 77%, 0.136 mmol scale). R_f (EtOAc/hexanes = 40:60) 0.7. mp: 108-110 ºC.

IR (DCM): 3357, 1741, 1518 cm^{-1}.

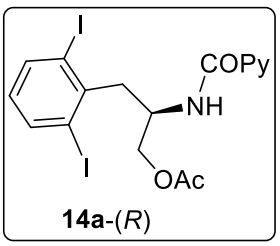
^{1}H NMR (400 MHz, $CDCl_3$): δ_H 8.59-8.57 (1H, m), 8.45 (1H, d, J = 9.6 Hz), 8.06 (1H, d, J = 7.8 Hz), 7.81-7.76 (3H, m), 7.43-7.39 (1H, m), 6.48 (1H, t, J = 7.9 Hz), 5.04-4.96 (1H, m), 4.39 (1H, dd, J_1 = 11.2 Hz, J_2 = 5.0 Hz), 4.27 (1H, dd, J_1 = 11.2 Hz, J_2 = 4.4 Hz), 3.56 (1H, dd, J_1 = 14.1 Hz, J_2 = 10.0 Hz), 3.42 (1H, dd, J_1 = 14.1 Hz, J_2 = 5.3 Hz), 2.13 (3H, s).

^{13}C{^{1}H} NMR (~101 MHz, $CDCl_3$): δ_C 171.0, 163.9, 149.4, 148.1, 141.8, 140.3, 137.2, 130.1, 126.2, 122.3, 100.4, 66.0, 48.2, 47.3, 21.1.

HRMS (ESI): *m/z* $(M + H)^+$ calcd for $C_{17}H_{17}I_2N_2O_3$: 550.9329 found: 550.9313.

The HPLC of compound **14a**-(RS) was determined by using the Daicel Chiralpak IC column, hexane/*i*-PrOH 50:50, flow rate 1.0 mL/min, UV detection at 254 nm, t_R = 10.85 min, t_S = 16.92 min.

(R)-3-(2,6-Diiodophenyl)-2-(picolinamido)propyl acetate (14a-(R)):



Compound **14a**-(R) was obtained from procedure H after purification by column chromatography on silica gel (EtOAc:hexanes = 40:60) as a colourless solid (83 mg, 75%, 0.20 mmol scale). R_f (EtOAc/hexanes = 40:60) 0.7. mp: 109-111 ºC.

IR (DCM): 3368, 1741, 1517 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ_H 8.58 (1H, d, J = 4.4 Hz), 8.44 (1H, d, J = 9.3 Hz), 8.05 (1H, d, J = 7.8 Hz), 7.81-7.76 (3H, m), 7.41 (1H, t, J = 6.1 Hz), 6.48 (1H, t, J = 7.8 Hz), 5.04-4.96

(1H, m), 4.39 (1H, dd, J_1 = 11.2 Hz, J_2 = 4.9 Hz), 4.27 (1H, dd, J_1 = 11.2 Hz, J_2 = 4.3 Hz), 3.56 (1H, dd, J_1 = 14.1 Hz, J_2 = 10.1 Hz), 3.42 (1H, dd, J_1 = 14.1 Hz, J_2 = 5.2 Hz), 2.13 (3H, s).

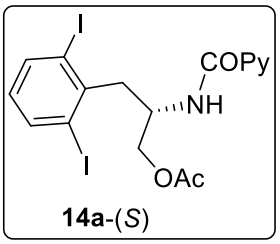
$^{13}C\{^1H\}$ NMR (~101 MHz, $CDCl_3$): δ_C 170.8, 163.8, 149.3, 148.0, 141.7, 140.2, 137.1, 130.0, 126.1, 122.1, 100.3, 65.6, 48.2, 47.2, 21.0.

HRMS (ESI): *m/z* $(M + H)^+$ calcd for $C_{17}H_{17}I_2N_2O_3$: 550.9329 found: 550.9343.

$(\alpha)^{25}_D$ = 146.2 (*c* = 0.02 g/mL, $CHCl_3$).

The enantiomeric ratio (*er* 99:1) of compound **14a**-(R) was determined by using the Daicel Chiralpak IC column, hexane/*i*-PrOH 50:50, flow rate 1.0 mL/min, UV detection at 254 nm, t_R = 11.43 min, t_S = 18.23 min.

(S)-3-(2,6-Diiodophenyl)-2-(picolinamido)propyl acetate (14a-(S)):



14a-(*S*)

Compound **14a**-(S) was obtained from procedure H after purification by column chromatography on silica gel (EtOAc:hexanes = 40:60) as a colourless solid (90 mg, 82%, 0.20 mmol scale). R_f (EtOAc/hexanes = 40:60) 0.7. mp: 108-110 ^oC.

IR (DCM): 3367, 1741, 1516 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ_H 8.59-8.57 (1H, m), 8.45 (1H, d, *J* = 9.5 Hz), 8.05 (1H, d, *J* = 7.8 Hz), 7.81-7.76 (3H, m), 7.42-7.39 (1H, m), 6.48 (1H, t, *J* = 7.8 Hz), 5.04-4.96 (1H, m), 4.39 (1H, dd, J_1 = 11.2 Hz, J_2 = 5.0 Hz), 4.27 (1H, dd, J_1 = 11.2 Hz, J_2 = 4.4 Hz), 3.56 (1H, dd, J_1 = 14.1 Hz, J_2 = 10.0 Hz), 3.42 (1H, dd, J_1 = 14.1 Hz, J_2 = 5.3 Hz), 2.13 (3H, s).

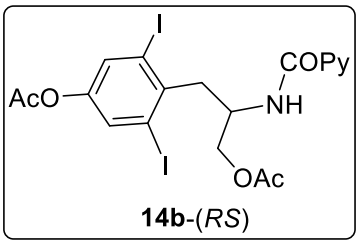
$^{13}C\{^1H\}$ NMR (~101 MHz, $CDCl_3$): δ_C 170.9, 163.8, 149.3, 148.0, 141.7, 140.2, 137.1, 130.0, 126.1, 122.2, 100.3, 65.9, 48.1, 47.2, 21.0.

HRMS (ESI): *m/z* $(M + H)^+$ calcd for $C_{17}H_{17}I_2N_2O_3$: 550.9329 found: 550.9349.

$(\alpha)^{25}_D$ = -155.2 (*c* = 0.02 g/mL, $CHCl_3$).

The enantiomeric ratio (*er* 99:1) of compound **14a**-(S) was determined by using the Daicel Chiralpak IC column, hexane/*i*-PrOH 50:50, flow rate 1.0 mL/min, UV detection at 254 nm, t_R = 10.72 min, t_S = 17.44 min.

3-(4-Acetoxy-2,6-diiodophenyl)-2-(picolinamido)propyl acetate (14b-(RS)):



14b-(*RS*)

Compound **14b**-(RS) was obtained from procedure H after purification by column chromatography on silica gel (EtOAc:hexanes = 50:50) as a colourless solid (41 mg, 67%, 0.1 mmol scale). R_f (EtOAc/hexanes = 50:50) 0.7; mp: 153-155 ^oC.

IR (DCM): 3339, 1738, 1527 cm^{-1}.

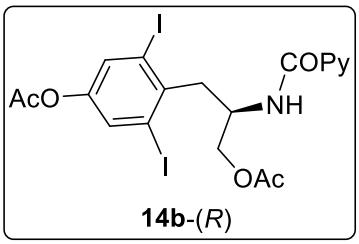
^{1}H NMR (400 MHz, $CDCl_3$): δ_H 8.59-8.57 (1H, m), 8.43 (1H, d, J = 9.6 Hz), 8.07 (1H, dt, J_1 = 7.8 Hz, J_2 = 1.0 Hz), 7.80 (1H, td, J_1 = 7.7 Hz, J_2 = 1.7 Hz), 7.58 (2H, s), 7.43-7.40 (1H, m), 5.00-4.94 (1H, m), 4.39 (1H, dd, J_1 = 11.2 Hz, J_2 = 5.0 Hz), 4.27 (1H, dd, J_1 = 11.3 Hz, J_2 = 4.5 Hz), 3.55 (1H, dd, J_1 = 14.2 Hz, J_2 = 9.9 Hz), 3.42 (1H, dd, J_1 = 14.2 Hz, J_2 = 5.4 Hz), 2.23 (3H, s), 2.13 (3H, s).

^{13}C{^{1}H} NMR (~101 MHz, $CDCl_3$): δ_C 170.9, 168.6, 163.9, 149.4, 148.9, 148.1, 139.4, 137.2, 133.3, 126.2, 122.3, 98.5, 65.9, 48.2, 46.5, 21.0, 21.0.

HRMS (ESI): *m/z* $(M + H)^+$ calcd for $C_{19}H_{19}I_2N_2O_5$: 608.9383; found: 608.9385.

The HPLC of compound **14b-**(RS) was determined by using the Daicel Chiralpak IA column, hexane/*i*-PrOH 90:10, flow rate 1.0 mL/min, UV detection at 254 nm, t_R = 18.86 min, t_S = 20.84 min.

(R)-3-(4-Acetoxy-2,6-diiodophenyl)-2-(picolinamido)propyl acetate (14b-(R)):



14b-(*R*)

Compound **14b**-(R) was obtained from procedure H after purification by column chromatography on silica gel (EtOAc:hexanes = 50:50) as a colourless solid (38 mg, 62%, 0.1 mmol scale). R_f (EtOAc/hexanes = 50:50) 0.7. mp: 154-156 ^{o}C; IR (DCM): 3342, 1738, 1527 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ_H 8.60-8.58 (1H, m), 8.44 (1H, d, J = 9.6 Hz), 8.08 (1H, d, J = 7.8 Hz), 7.82 (1H, td, J_1 = 7.7 Hz, J_2 = 1.7 Hz), 7.59 (2H, s), 7.44-7.41 (1H, m), 5.02-4.95 (1H, m), 4.40 (1H, dd, J_1 = 11.3 Hz, J_2 = 5.0 Hz), 4.28 (1H, dd, J_1 = 11.2 Hz, J_2 = 4.5 Hz), 3.56 (1H, dd, J_1 = 14.2 Hz, J_2 = 9.9 Hz), 3.43 (1H, dd, J_1 = 14.2 Hz, J_2 = 5.4 Hz), 2.24 (3H, s), 2.14 (3H, s).

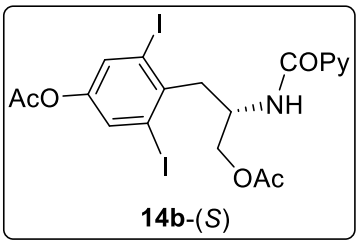
^{13}C{^{1}H} NMR (~101 MHz, $CDCl_3$): δ_C 170.9, 168.5, 163.9, 149.4, 148.9, 148.1, 139.4, 137.2, 133.3, 126.2, 122.3, 98.5, 65.9, 48.2, 46.5, 21.0, 20.9.

HRMS (ESI): *m/z* $(M + H)^+$ calcd for $C_{19}H_{19}I_2N_2O_5$: 608.9383; found: 608.9377.

$(\alpha)^{25}_D$ = 115.9 (c = 0.02 g/mL, $CHCl_3$).

The enantiomeric ratio (*er* 99:1) of compound **14b**-(R) was determined by using the Daicel Chiralpak IA column, hexane/*i*-PrOH 90:10, flow rate 1.0 mL/min, UV detection at 254 nm, t_R = 17.48 min, t_S = 20.91 min.

(S)-3-(4-Acetoxy-2,6-diiodophenyl)-2-(picolinamido)propyl acetate (14b-(S)):



14b-(*S*)

Compound **14b**-(S) was obtained from procedure H after purification by column chromatography on silica gel (EtOAc:hexanes = 50:50) as a colourless solid (45 mg, 74%, 0.1 mmol scale). R_f (EtOAc/hexanes = 50:50) 0.7. mp: 155-157 ºC. IR (DCM): 3339, 1738, 1527 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ_H 8.56 (1H, d, J = 4.7 Hz), 8.42 (1H, d, J = 9.5 Hz), 8.07 (1H, d, J = 7.8 Hz), 7.80 (1H, td, J_1 = 7.7 Hz, J_2 = 1.2 Hz), 7.58 (2H, s), 7.43-7.40 (1H, m), 5.00-4.94 (1H, m), 4.38 (1H, dd, J_1 = 11.2 Hz, J_2 = 5.0 Hz), 4.26 (1H, dd, J_1 = 11.2 Hz, J_2 = 4.5 Hz), 3.55 (1H, dd, J_1 = 14.2 Hz, J_2 = 9.9 Hz), 3.41 (1H, dd, J_1 = 14.2 Hz, J_2 = 5.4 Hz), 2.23 (3H, s), 2.12 (3H, s).

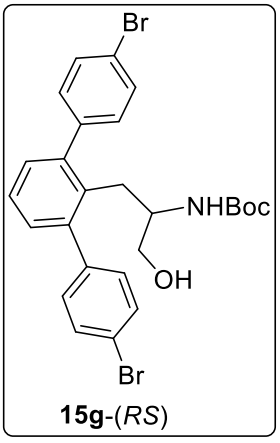
$^{13}C\{^1H\}$ NMR (~101 MHz, $CDCl_3$): δ_C 170.9, 168.6, 163.9, 149.4, 148.9, 148.1, 139.4, 137.2, 133.3, 126.2, 122.3, 98.5, 65.9, 48.2, 46.5, 21.0, 20.9.

HRMS (ESI): *m/z* $(M + H)^+$ calcd for $C_{19}H_{19}I_2N_2O_5$: 608.9383; found: 608.9362.

$(\alpha)^{25}_D$ = -113.9 (c = 0.02 g/mL, $CHCl_3$).

The enantiomeric ratio (*er* 98:2) of compound **14b**-(S) was determined by using the Daicel Chiralpak IA column, hexane/*i*-PrOH 90:10, flow rate 1.0 mL/min, UV detection at 254 nm, t_R = 17.93 min, t_S = 21.59 min.

***Tert*-butyl (1-(4,4''-dibromo-(1,1':3',1''-terphenyl)-2'-yl)-3-hydroxypropan-2-yl)carbamate (15g-(RS)):**



15g-(*RS*)

Compound **15g**-(RS) was obtained from procedures K and M after purification by column chromatography on silica gel (EtOAc:hexanes = 20:80) as a yellow coloured semi-solid (50 mg, 45%, 0.20 mmol scale). R_f (EtOAc/hexanes = 20:80) 0.6.

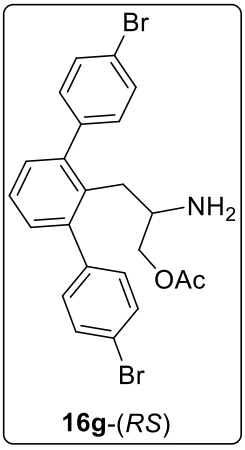
IR (DCM): 3437, 1701, 1499 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ_H 7.56 (4H, d, J = 8.4 Hz), 7.28-7.26 (1H, m), 7.27 (4H, d, J = 8.0 Hz), 7.16 (2H, d, J = 7.5 Hz), 3.94 (1H, d, J = 8.6 Hz), 3.33 (1H, br. s), 3.12 (1H, dd, J_1 = 11.0 Hz, J_2 = 3.9 Hz), 2.98 (1H, dd, J_1 = 10.7 Hz, J_2 = 5.4 Hz), 2.83 (1H, dd, J_1 = 14.0 Hz, J_2 = 4.5 Hz), 2.76-2.68 (1H, m), 1.30 (9H, s). (One of the labile proton signals of either NH or OH could not be ascertained).

$^{13}C\{^1H\}$ NMR (~101 MHz, $CDCl_3$): δ_C 155.4, 142.4, 140.9, 133.1, 131.6, 131.3, 129.8, 126.3, 121.4, 79.3, 65.6, 53.2, 31.1, 28.3.

HRMS (ESI): *m/z* $(M + Na)^+$ calcd for $C_{26}H_{27}Br_2NNaO_3$: 582.0255 found: 582.0265.

2-Amino-3-(4,4''-dibromo-(1,1':3',1''-terphenyl)-2'-yl)propyl acetate (16g-(RS)):



Compound **16g**-(RS) was obtained from procedure L after purification by column chromatography on silica gel (EtOAc:hexanes = 50:50) as a colourless solid (30 mg, 60%, 0.1 mmol scale). R_f (EtOAc/hexanes = 50:50) 0.6. mp: 180-182 °C.

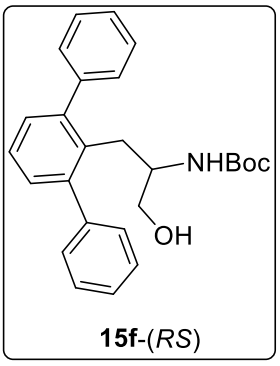
IR (DCM): 3367, 1655, 1536 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ_H 7.58 (4H, dt, J = 8.4 Hz), 7.32-7.27 (1H, m), 7.26 (4H, dt, J = 8.4 Hz), 7.17 (2H, d, J = 7.6 Hz), 4.98 (1H, d, J = 8.1 Hz), 3.60-3.55 (1H, m), 3.13 (1H, dd, J_1 = 11.1 Hz, J_2 = 4.0 Hz), 2.99 (1H, dd, J_1 = 11.1 Hz, J_2 = 5.2 Hz), 2.90-2.88 (2H, m), 2.17 (1H, br. s), 1.70 (3H, s). (While the integration accounts for all expected protons, in the proton NMR spectrum, the labile proton signal of NH_2 could not be ascertained).

$^{13}C\{^1H\}$ NMR (~101 MHz, $CDCl_3$): δ_C 170.2, 142.2, 140.8, 133.0, 131.7, 131.2, 130.0, 126.6, 121.6, 65.2, 52.7, 30.5, 23.3.

HRMS (ESI): *m/z* $(M + H)^+$ calcd for $C_{23}H_{22}Br_2NO_2$: 502.0017 found: 502.0010.

***Tert*-butyl (1-((1,1':3',1''-terphenyl)-2'-yl)-3-hydroxypropan-2-yl)carbamate (15f -(RS)):**



Compound **15f**-(RS) was obtained from procedures L and M after purification by column chromatography on silica gel (EtOAc:hexanes = 20:80) as a colourless solid (120 mg, 58%, 0.5 mmol scale). R_f (EtOAc/hexanes = 20:80) 0.5. mp: 96-98 °C.

IR (DCM): 3431, 1703, 1504 cm^{-1}.

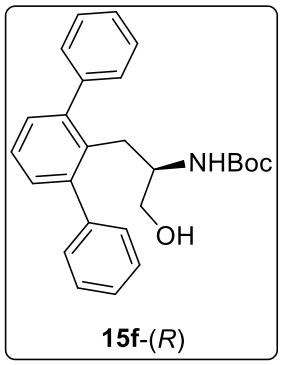
^1H NMR (400 MHz, $CDCl_3$): δ_H 7.46-7.34 (10H, m), 7.32-7.28 (1H, m), 7.22-7.20 (2H, m), 3.97-3.95 (1H, m), 3.25 (1H, br. s), 3.06 (1H, dd, J_1 = 11.0 Hz, J_2 = 4.1 Hz), 2.97-2.88 (2H, m), 2.77-2.71 (1H, m), 1.32 (9H, s). (One of the labile proton signals of either NH or OH could not be ascertained).

$^{13}C\{^1H\}$ NMR (~101 MHz, $CDCl_3$): δ_C 155.8, 143.4, 142.1, 133.2, 129.6, 129.6, 128.4, 127.2, 126.1, 79.1, 65.9, 53.6, 30.8, 28.3.

HRMS (ESI): *m/z* $(M + Na)^+$ calcd for $C_{26}H_{29}NNaO_3$: 426.2045 found: 426.2039.

The HPLC of compound **15f**-(RS) was determined by using the Daicel Chiralpak IC column, hexane/*i*-PrOH 90:10, flow rate 1.0 mL/min, UV detection at 254 nm, t_R = 13.47 min, t_S = 19.27 min.

(R)-*Tert*-butyl (1-((1,1':3',1''-terphenyl)-2'-yl)-3-hydroxypropan-2-yl)carbamate (15f-(R)):



15f-(*R*)

Compound **15f**-(R) was obtained from procedures M and L after purification by column chromatography on silica gel (EtOAc:hexanes = 20:80) as a colourless solid (107 mg, 52%, 0.5 mmol scale). R_f (EtOAc/hexanes = 20:80) 0.5. mp: 98-100 ^oC.

IR (DCM): 3435, 1703, 1504 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ_H 7.46-7.34 (10H, m), 7.32-7.28 (1H, m), 7.22-7.20 (2H, m), 3.95 (1H, d, J = 7.6 Hz), 3.33 (1H, br. s), 3.06 (1H, dd, J_1 = 11.0 Hz, J_2 = 4.0 Hz), 2.97-2.88 (2H, m), 2.77-2.71 (1H, m), 1.32 (9H, s). (One of the labile proton signals of either NH or OH could not be ascertained).

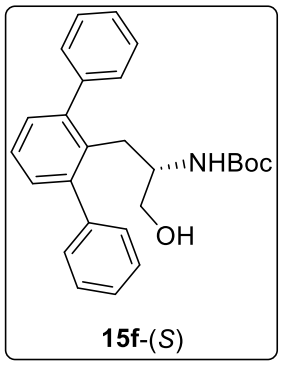
$^{13}C\{^1H\}$ NMR (~101 MHz, $CDCl_3$): δ_C 155.8, 143.4, 142.1, 133.2, 129.6, 129.6, 128.4, 127.2, 126.1, 79.1, 65.9, 53.6, 30.8, 28.3.

HRMS (ESI): *m/z* $(M + Na)^+$ calcd for $C_{26}H_{29}NNaO_3$: 426.2045 found: 426.2037.

$(\alpha)^{25}_D$ = 12.0 (c = 0.03 g/mL, $CHCl_3$).

The enantiomeric ratio (*er* 99:1) of compound **15f**-(R) was determined by using the Daicel Chiralpak IC column, hexane/*i*-PrOH 90:10, flow rate 1.0 mL/min, UV detection at 254 nm, t_R = 13.88 min, t_S = 19.95 min.

(S)-*Tert*-butyl (1-((1,1':3',1''-terphenyl)-2'-yl)-3-hydroxypropan-2-yl)carbamate (15f-(S)):



15f-(*S*)

Compound **15f**-(S) was obtained from procedures L and M after purification by column chromatography on silica gel (EtOAc:hexanes = 20:80) as a colourless solid (110 mg, 54%, 0.5 mmol scale). R_f (EtOAc/hexanes = 20:80) 0.5. mp: 97-99 ^oC.

IR (DCM): 3431, 1706, 1507 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ_H 7.46-7.34 (10H, m), 7.32-7.28 (1H, m), 7.21 (2H, d, J = 7.2 Hz), 3.96 (1H, d, J = 7.4 Hz), 3.32 (1H, br. s), 3.05 (1H, dd, J_1 = 11.0 Hz, J_2 = 4.2 Hz), 2.97-2.88 (2H, m), 2.77-2.71 (1H, m), 1.32 (9H, s).

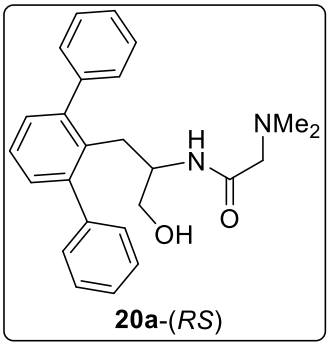
$^{13}C\{^1H\}$ NMR (~101 MHz, $CDCl_3$): δ_C 155.8, 143.4, 142.1, 133.2, 129.6, 128.4, 127.2, 126.1, 79.1, 65.8, 53.6, 30.9, 28.3.

HRMS (ESI): *m/z* $(M + Na)^+$ calcd for $C_{26}H_{29}NNaO_3$: 426.2045 found: 426.2043.

$(\alpha)^{25}_D$ = -12.7 (c = 0.03 g/mL, $CHCl_3$).

The enantiomeric ratio (*er* 99:1) of compound **15f**-(S) was determined by using the Daicel Chiralpak IC column, hexane/*i*-PrOH 90:10, flow rate 1.0 mL/min, UV detection at 254 nm, t_R = 13.68 min, t_S = 19.55 min.

_N_-(1-((1,1':3',1''-Terphenyl)-2'-yl)-3-hydroxypropan-2-yl)-2-(dimethylamino)acetamide (20a-(RS)):



20a-(*RS*)

Compound **20a**-(RS) was obtained from procedures L and N after purification by column chromatography on silica gel (MeOH:EtOAc = 20:80) as a colourless semi-solid (49 mg, 52%, 0.24 mmol scale). R_f (MeOH:EtOAc = 20:80) 0.2.

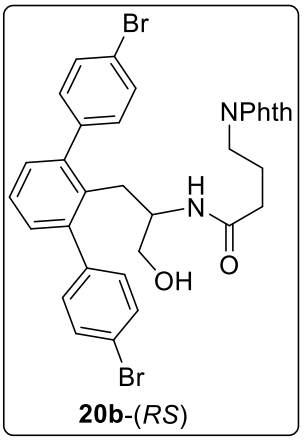
IR (DCM): 3359, 1662, 1523 cm^{-1}.

^{1}H NMR (400 MHz, DMSO-d_6): δ_H 7.48-7.44 (4H, m), 7.40-7.37 (6H, m), 7.29 (1H, t, *J* = 7.7 Hz), 7.13 (2H, d, *J* = 7.5 Hz), 6.45 (1H, d, *J* = 8.7 Hz), 4.38 (1H, t, *J* = 5.2 Hz), 2.97 (1H, dd, J_1 = 14.4 Hz, J_2 = 4.4 Hz), 2.87-2.81 (2H, m), 2.77-2.71 (1H, m), 2.63 (1H, d, *J* = 15.5 Hz), 2.55 (1H, d, *J* = 15.5 Hz), 2.51-2.50 (1H, m), 2.00 (6H, s).

^{13}C NMR (~101 MHz, DMSO-d_6): δ_C 169.0, 143.6, 142.3, 134.2, 129.8, 129.7, 128.7, 127.4, 126.4, 63.8, 63.2, 50.6, 45.7, 31.3.

HRMS (ESI): *m/z* $(M + H)^+$ calcd for $C_{25}H_{29}N_2O_2$: 389.2229 found: 389.2236.

_N_-(1-(4,4''-Dibromo-(1,1':3',1''-terphenyl)-2'-yl)-3-hydroxypropan-2-yl)-4-(1,3-dioxoisoindolin-2-yl)butanamide (20b-(RS)):



20b-(*RS*)

Compound **20b**-(RS) was obtained from procedures L and N after purification by column chromatography on silica gel (EtOAc:hexanes = 20:80) as a colourless solid (35 mg, 51%, 0.1 mmol scale). R_f (EtOAc/hexanes = 20:80) 0.3. mp: 112-114 ^{o}C.

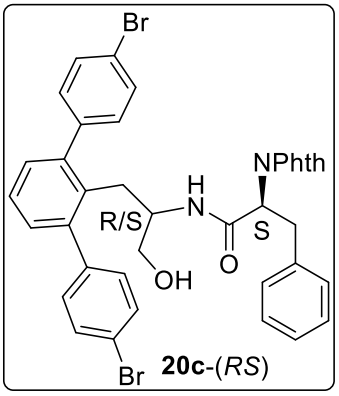
IR (DCM): 3391, 1707, 1394 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ_H 7.84 (2H, dd, J_1 = 5.4 Hz, J_2 = 3.0 Hz), 7.74 (2H, dd, J_1 = 5.4 Hz, J_2 = 3.0 Hz), 7.54 (4H, dt, J_1 = 8.4 Hz, J_2 = 2.3 Hz), 7.29-7.23 (5H, m), 7.15 (2H, d, *J* = 7.5 Hz), 5.21 (1H, d, *J* = 8.3 Hz), 3.67-3.62(1H, m), 3.59-3.56 (2H, m), 3.23 (dd, 1H, J_1 = 11.1 Hz, J_2 = 2.5 Hz), 3.00-2.89 (3H, m), 2.53 (1H, br. s), 2.01-1.76 (4H, m).

^{13}C{^{1}H} NMR (~101 MHz, $CDCl_3$): δ_C 171.7, 168.7, 142.2, 140.8, 134.2, 133.2, 131.9, 131.6, 131.2, 129.9, 126.5, 123.4, 121.4, 65.2, 52.8, 36.9, 33.6, 30.5, 24.7.

HRMS (ESI): *m/z* $(M + H)^+$ calcd for $C_{33}H_{29}Br_2N_2O_4$: 675.0494 found: 675.0479.

(2S)-*N*-(1-(4,4''-Dibromo-(1,1':3',1''-terphenyl)-2'-yl)-3-hydroxypropan-2-yl)-2-(1,3-dioxoisoindolin-2-yl)-3-phenylpropanamide (20c-(RS)):



Compound **20c**-(RS) was obtained from procedures L and N after purification by column chromatography on silica gel (EtOAc:hexanes = 30:70) as a colourless solid (47 mg, 64%, 0.1 mmol scale, mixture of diastereomers). R_f (EtOAc/hexanes = 30:70) 0.3. mp: 106-108 ^oC.

IR (DCM): 3436, 1712, 1502 cm^{-1}.

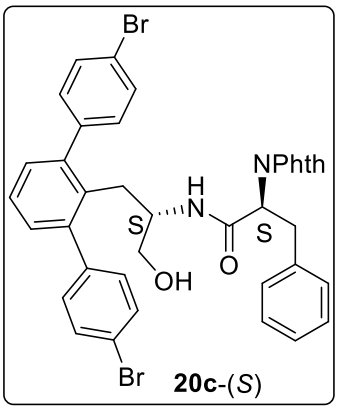
^1H NMR (400 MHz, $CDCl_3$): δ_H 7.75-7.70 (8H, m), 7.59 (4H, d, J = 8.3 Hz), 7.45 (3H, d, J = 8.3 Hz), 7.26-6.99 (27H, m), 5.29-5.26 (2H, m), 4.85-4.79 (2H, m), 3.73-3.67 (1H, m), 3.50-3.41 (2H, m), 3.30-3.14 (5H, m), 3.06-2.78 (6H, m). (Proton NMR values correspond to a mixture of diastereomers).

$^{13}C\{^1H\}$ NMR (~101 MHz, $CDCl_3$): δ_C 168.4, 168.1, 167.7, 167.5, 142.2, 140.5, 140.4, 136.6, 136.4, 134.5, 134.2, 132.4, 132.3, 131.7, 131.6, 131.3, 131.0, 131.0, 129.9, 129.8, 128.9, 128.8, 128.6, 128.5, 127.0, 126.9, 126.6, 126.5, 123.6, 123.5, 121.6, 121.4, 65.1, 64.8, 55.3, 55.2, 52.9, 52.4, 34.8, 34.6, 30.3, 30.2. (All the signals of corresponding to both diastereomers are listed).

HRMS (ESI): *m/z* $(M + H)^+$ calcd for $C_{38}H_{31}Br_2N_2O_4$: 737.0651 found: 737.0640.

The diastereomeric ratio (*dr* 44:56 (*R,S*:*S,S*)) of **20c**-(RS) was determined by using the Daicel Chiralpak IA column, hexane/*i*-PrOH 90:10, flow rate 1.0 mL/min, UV detection at 254 nm, $t_{R,S}$ = 14.42 min, $t_{S,S}$ = 16.17 min.

(S)-*N*-((S)-1-(4,4''-Dibromo-(1,1':3',1''-terphenyl)-2'-yl)-3-hydroxypropan-2-yl)-2-(1,3-dioxoisoindolin-2-yl)-3-phenylpropanamide (20c-(S)):



Compound **20c**-(S) was obtained from procedures L and N after purification by column chromatography on silica gel (EtOAc:hexanes = 30:70) as a colourless solid (47 mg, 63%, 0.10 mmol scale). R_f (EtOAc/hexanes = 30:70) 0.3. mp: 107-109 ^oC.

IR (DCM): 3422, 1713, 1501 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ_H 7.75-7.69 (4H, m), 7.58 (4H, d, J = 8.1 Hz), 7.22-6.97 (13H, m), 5.28 (1H, d, J = 7.2 Hz), 4.83-4.79 (1H, m), 3.47-3.46 (1H, m), 3.34-3.23 (2H, m), 3.17-3.14

(1H, m), 3.04 (1H, dd, J_1 = 11.2 Hz, J_2 = 5.2 Hz), 2.94-2.85 (2H, m). (Proton NMR values correspond to major diastereomers).

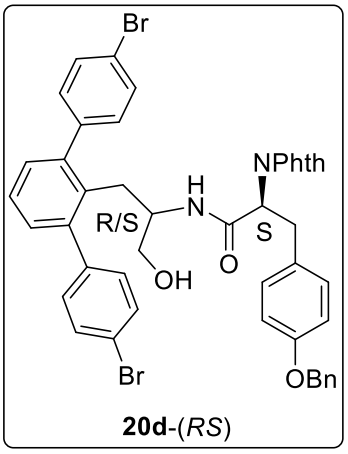
$^{13}C\{^1H\}$ NMR (~101 MHz, $CDCl_3$): δ_C 168.4, 167.5, 142.2, 140.5, 140.4, 136.6, 136.4, 134.5, 134.2, 132.3, 131.7, 131.6, 131.3, 131.0, 129.9, 129.8, 128.9, 128.8, 128.6, 128.5, 127.0, 126.9, 126.5, 123.6, 123.5, 121.6, 121.4, 65.1, 55.2, 52.8, 34.6, 30.2. (A few of the signals corresponding to traces of the minor diastereomer were also observed).

HRMS (ESI): *m/z* $(M + H)^+$ calcd for $C_{38}H_{31}Br_2N_2O_4$: 737.0651 found: 737.0638.

$(\alpha)^{25}_D$ = -40.0 (*c* = 0.02 g/mL, $CHCl_3$).

The diastereomeric ratio (*dr* 1:99 (*R,S*:*S,S*)) of compound **20c**-(S) was determined by using the Daicel Chiralpak IA column, hexane/*i*-PrOH 90:10, flow rate 1.0 mL/min, UV detection at 254 nm, $t_{R,S}$ = 14.55 min, $t_{S,S}$ = 16.11 min.

(2S)-3-(4-(Benzyloxy)phenyl)-*N*-(1-(4,4''-dibromo-(1,1':3',1''-terphenyl)-2'-yl)-3-hydroxypropan-2-yl)-2-(1,3-dioxoisoindolin-2-yl)propanamide (**20d-(RS)):**



20d-(*RS*)

Compound **20d**-(RS) was obtained from procedures L and N after purification by column chromatography on silica gel (EtOAc:hexanes = 30:70) as a colourless solid (56 mg, 67%, 0.10 mmol scale, mixture of diastereomers). R_f (EtOAc/hexanes = 30:70) 0.3. mp: 102-104 °C.

IR (DCM): 3412, 1711, 1507 cm^{-1}.

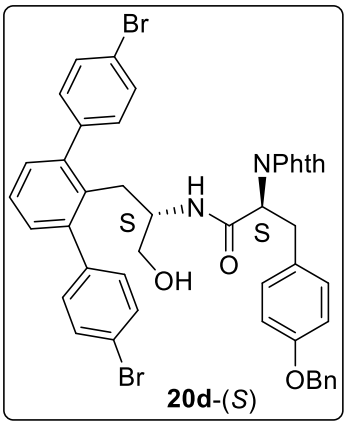
^1H NMR (400 MHz, $CDCl_3$): δ_H 7.75-7.68 (8H, m), 7.57 (5H, d, *J* = 8.3 Hz), 7.44 (3H, d, *J* = 8.2 Hz), 7.35-7.29 (11H, m), 7.25-7.17 (10H, m), 7.10 (2H, d, *J* = 7.6 Hz), 7.01-6.90 (8H, m), 6.77 (2H, d, *J* = 8.6 Hz), 6.70 (1H, d, *J* = 8.6 Hz), 5.31 (2H, d, *J* = 7.7 Hz), 4.97-4.85 (4H, m), 4.80-4.74 (2H, m), 3.71-3.67 (1H, m), 3.49-3.47 (1H, m), 3.23 (1H, dd, J_1 = 14.2 Hz, J_2 = 5.2 Hz), 3.25-3.20 (3H, m), 3.16-3.10 (2H, m), 3.04-2.76 (6H, m). (Proton NMR values correspond to major diastereomers).

$^{13}C\{^1H\}$ NMR (~101 MHz, $CDCl_3$): δ_C 168.4, 168.2, 167.7, 167.6, 157.6, 157.5, 142.1, 142.1, 140.5, 140.4, 136.8, 134.5, 134.1, 132.4, 132.3, 131.6, 131.6, 131.3, 131.0, 131.0, 129.9, 129.8, 129.8, 128.8, 128.6, 128.5, 127.8, 127.3, 126.5, 126.4, 123.6, 123.4, 121.5, 121.3, 114.9, 114.8, 69.8, 69.8, 65.0, 64.7, 55.4, 55.3, 52.8, 52.4, 33.9, 33.8, 30.3, 30.2. (All the signals corresponding to both diastereomers are listed).

HRMS (ESI): *m/z* $(M + Na)^+$ calcd for $C_{45}H_{36}Br_2N_2NaO_5$: 865.0889 found: 865.0904.

The diastereomeric ratio (*dr* 42:58 (*R,S*:*S,S*)) compound **20d**-(RS) was determined by using the Daicel Chiralpak IA column, hexane/*i*-PrOH 90:10, flow rate 1.0 mL/min, UV detection at 254 nm, $t_{R,S}$ = 20.04 min, $t_{S,S}$ = 28.23 min.

(S)-3-(4-(Benzyloxy)phenyl)-*N*-((S)-1-(4,4''-dibromo-(1,1':3',1''-terphenyl)-2'-yl)-3-hydroxypropan-2-yl)-2-(1,3-dioxoisoindolin-2-yl)propenamide (**20d-(S)**):



Compound **20d**-(S) was obtained from procedures L and N after purification by column chromatography on silica gel (EtOAc:hexanes = 30:70) as a colourless solid (53 mg, 63%, 0.10 mmol scale). R_f (EtOAc/hexanes = 30:70) 0.3. mp: 101-103 °C. IR (DCM): 3422 1710, 1506 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ_H 7.75-7.69 (4H, m), 7.58 (4H, d, *J* = 8.2 Hz), 7.36-7.20 (10H, m), 7.03-6.95 (5H, m), 6.77 (2H, d, *J* = 8.4 Hz), 5.29 (1H, d, *J* = 7.2 Hz), 4.98-4.92 (2H, m), 4.78-4.74 (1H, m), 3.50-3.47 (1H, m), 3.23-3.20 (2H, m), 3.17-3.13 (1H, m), 3.04 (1H, dd, J_1 = 11.2 Hz, J_2 = 5.3 Hz), 2.94-2.88 (2H, m). (Proton NMR values correspond to major diastereomers).

$^{13}C\{^1H\}$ NMR (~101 MHz, $CDCl_3$): δ_C 168.5, 167.6, 157.6, 142.1, 140.4, 136.8, 134.2, 132.3, 131.7, 131.3, 131.0, 129.8, 128.6, 128.5, 127.9, 127.4, 126.5, 123.5, 121.6, 115.0, 69.8, 65.1, 55.3, 52.9, 33.8, 30.2.

HRMS (ESI): *m/z* $(M + Na)^+$ calcd for $C_{45}H_{36}Br_2N_2NaO_5$: 865.0889 found: 865.0911.

$(\alpha)^{25}_D$ = -65.1 (*c* = 0.02, $CHCl_3$).

The diastereomeric ratio (*dr* 1:99 (*R,S*:*S,S*)) compound **20d**-(S) was determined by using the Daicel Chiralpak IA column, hexane/*i*-PrOH 90:10, flow rate 1.0 mL/min, UV detection at 254 nm, $t_{R,S}$ = 20.25 min, $t_{S,S}$ = 28.23 min.

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[28] (a) There can be two scenarios with regard to the functionalization of δ-C-H bonds in substrates. In the first case, a substrate that has no γ-C-H bond but has a δ-C-H bond and is subjected to the δ-C-H functionalization. In the second case, a substrate

that has a γ-C-H bond and a δ-C-H bond and is subjected to the regioselective δ-C-H functionalization. In general, both scenarios comprising of functionalization of δ-C-H bonds are challenging. Nonetheless, the second case comprising selective functionalization of the δ-C-H bond in a substrate which also has a γ-C-H bond is an arduous task. The current work deals with the functionalization of the δ-C-H bond in a substrate which does not possess a γ-C-H bond.

[29] For selected references dealing with functionalization of δ-C-H bond in a substrate which does not possess a γ-C-H bond, see ref.[9-17,19a]

[30] For selected reference dealing with selective functionalization of the δ-C-H bond in a substrate that also has a γ-C-H bond, see ref.[18a]

Chapter 5
Construction of *β*-Phenylalanine Derivatives *via* Pd-Catalyzed, C(sp^2)-H (*ortho*) Functionalization.

For the purpose of this thesis work, the work of chapter 5 is re-used (adapted) with the permission from the publication; Narang, U [#].; Singh, P [#]., Babu, S. A[*]. *Eur. J. Org. Chem*. **2023**, e202300463. Title: Construction of *β*-Phenylalanine Derivatives *via* Pd-Catalyzed, C(sp^2)-H (*ortho*) Functionalization. (# = authors contributed equally).

The transition metal-catalyzed C-H activation and functionalization transformations have emerged as a prominent synthetic tool for the construction of functionalized small organic molecules.[1-4] The directing group (DG)-assisted site-selective C-H functionalization route enables the installation of functional groups at the targeted C-H bonds in organic molecules.[3,4] Especially, the Pd(II)-catalyzed bidentate directing group (DG)-aided C-H functionalization of carboxylic acid or amine substrates or amino acid derivatives has received considerable attention in recent years.[3,4] Accordingly, there has been a persistent effort to utilize the capability of the bidentate DG-aided site-selective C–H functionalization of various substrates.[3-9] In general, the site-selective C-H functionalization of carboxylic acid substrates using 8-aminoquinoline type DGs[3-5] and amine substrates using picolinamide type DGs[3,4,6-9] have emerged as reliable synthetic methods.

Unnatural (non-proteinogenic) amino acid derivatives are key motifs in various natural products, pharmaceuticals and synthetic drug molecules.[10] Especially, *β*-amino acids and *β*-peptides have received widespread attention in chemical, biological sciences and medicinal chemistry.[11] Consequently, the utilization of *β*-amino acid derivatives in designing peptidomimetics, in the synthesis of *β*-amino acid-based bioactive molecules and their incorporation into proteins are important research topics.[11-16] Of particular interest, *β*-Phenylalanine (3-amino-3-phenylpropionic acid) is an arylated *β*-amino acid motif, which is present in various natural products and bioactive molecules (Figure 1).[13-16] It is an important precursor in the synthesis of medicinally active molecules including peptides. Consequently, the synthesis of the *β*-phenylalanine derivatives has received considerable attention.[13-16] Along this line, 3-amino-3-phenylpropanols (which are the derivatives of *β*-phenylalanines and belong to 1,3-amino alcohol family) are versatile building blocks in the synthesis of medicinally active compounds.[13c,16a,17,18] (figure 1).

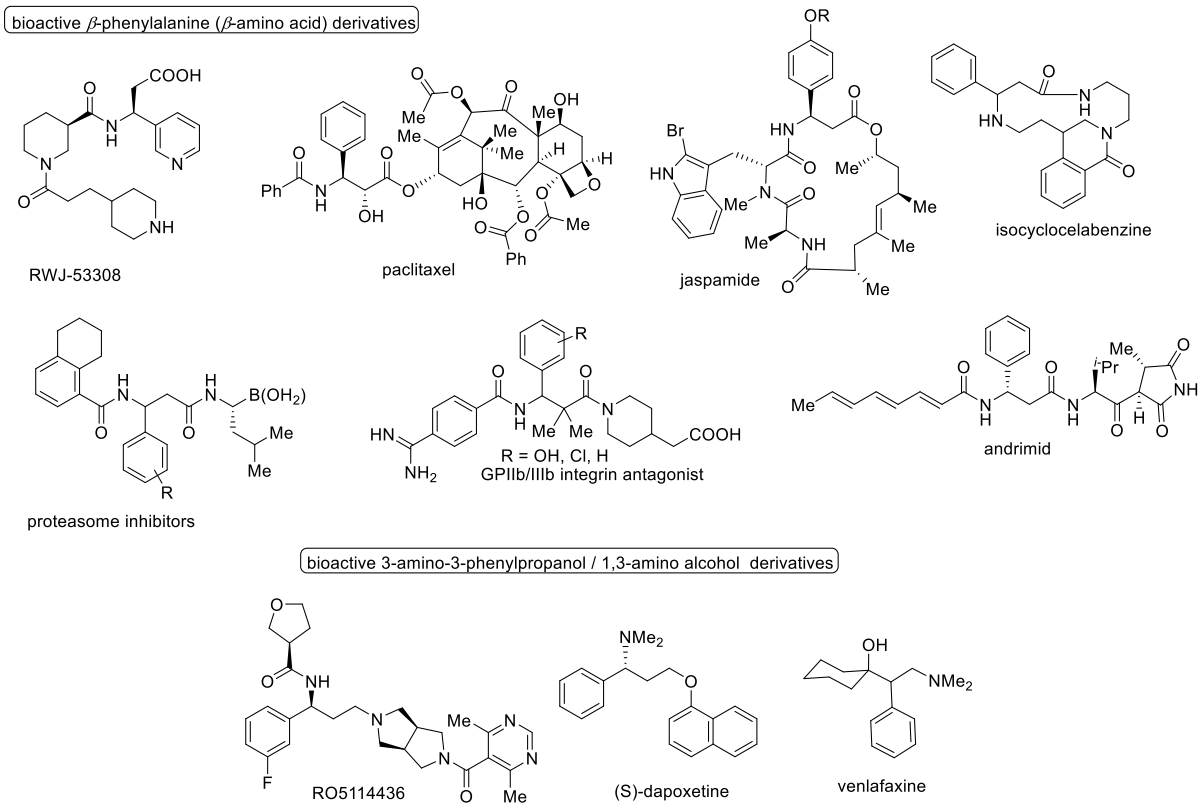
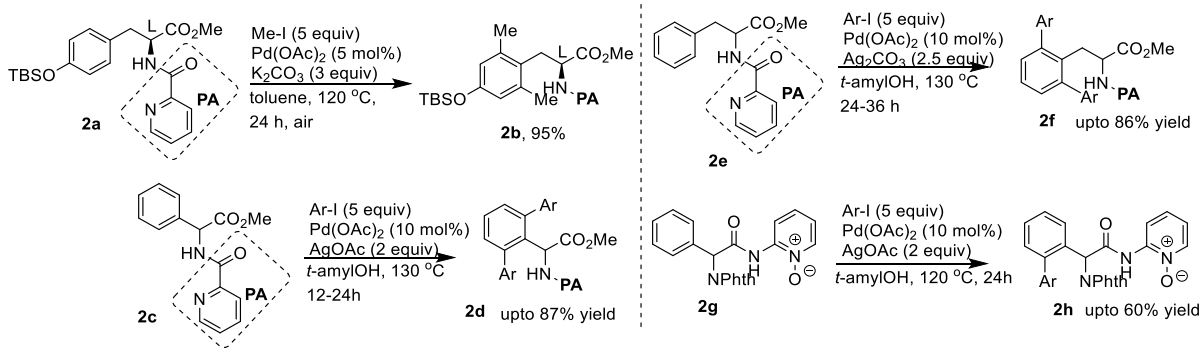


Figure 1: Examples of bioactive *β*-phenylalanine and 3-amino-3-phenylpropanol motif-containing compounds.

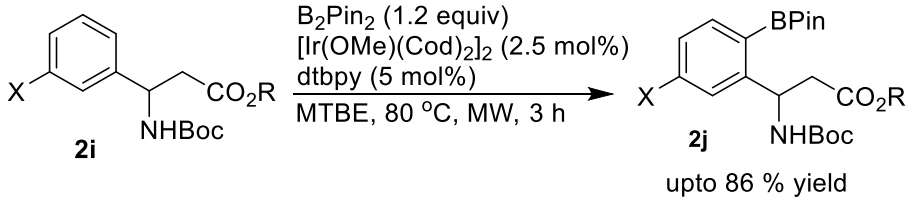
The Pd(II)-catalyzed directing group assisted C-H functionalization protocol has been well explored for achieving site-selective C-H functionalization of aliphatic[4] and various aromatic amino acids[4, 9] such as phenylglycine, phenylalanine, and tyrosine. In 2017[8a] Ma's group reported picolinamide directed a simple and efficient approach for *ortho*-C-H methylation of (*S*)-tyrosine moiety. The reaction method utilizes substrate **2a** (1 equiv), $Pd(OAc)_2$ (5 mol%), Me-I (5 equiv), K_2CO_3 (3 equiv) in toluene at 120 ^oC for 24 h under air to accomplish the desired methylated product **2b**. The reaction works well in a high scale without disturbing the stereochemistry of the product. Jiang and co-workers in 2018[9d] demonstrated Pd(II)-catalyzed *ortho*-C-H functionalization of phenylglycine and phenylalanine moiety using picolinamide as a directing group. With regard to C-H functionalization of phenylglycine, authors have explored arylation, alkylation, alkynylation, halogenation, alkoxylation, and acyloxylation under different conditions (Scheme 1a). This reaction protocol offers broad substrate scope, high functional group tolerance, and high selectivity. Authors have also carried out C-H arylation of phenylalanine at remote *δ*-(sp^2)-H position in good to excellent yield (Scheme 1a). In 2022[9b] our group has also reported an exciting method for mono *ortho*-C-H arylation of phenylglycine using pyridine-*N*-oxide as an inexpensive directing group. The optimum

reaction condition for mono C-H arylation consists of substrate **2g** (1 equiv), $Pd(OAc)_2$ (10 mol%), AgOAc (2 equiv), Ar-I (5 equiv), *t*-amylOH at 120 °C for 24 h to accomplish the mono arylated product **2h** in moderate to good yield having a wide range of aryl iodide scope (Scheme 1a).



Scheme 1a: Representative examples related to C-H functionalization of α-amino acids.

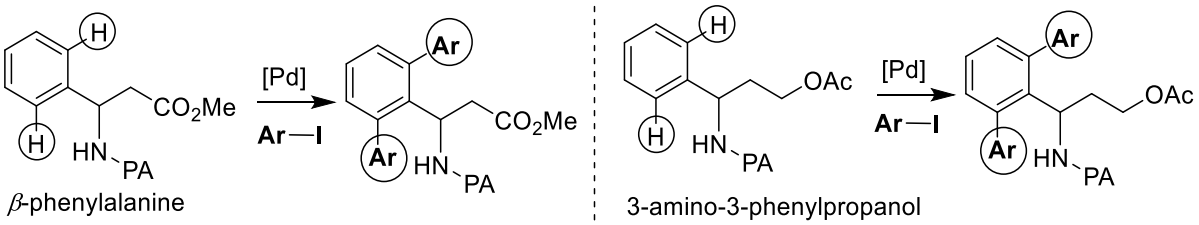
A literature survey revealed that Norticliffe and co-workers in 2020[19] reported an iridium-catalyzed regioselective C-H borylation of β-aryl-aminopropionic acid derivatives, which led to the construction of 3,5-functionalized protected β-aryl-aminopropionic acid boronates. The reaction method utilizes substrate **2i** (1 equiv), $[Ir(OMe)(cod)_2]_2$ (2.5 mol%), dtbpy (5 mol%), B_2Pin_2 (1.2 equiv) in MTBE as a solvent at 80 °C under microwave for 3 h to access borylated product **2j**. Authors have also demonstrated the versatility of the reaction through a sequential one pot reaction which could be applied to the synthesis of diverse building blocks for numerous bio-active molecules (Scheme 1b).



Scheme 1b: Representative example related to C-H functionalization of β-aryl-aminopropionic acid.

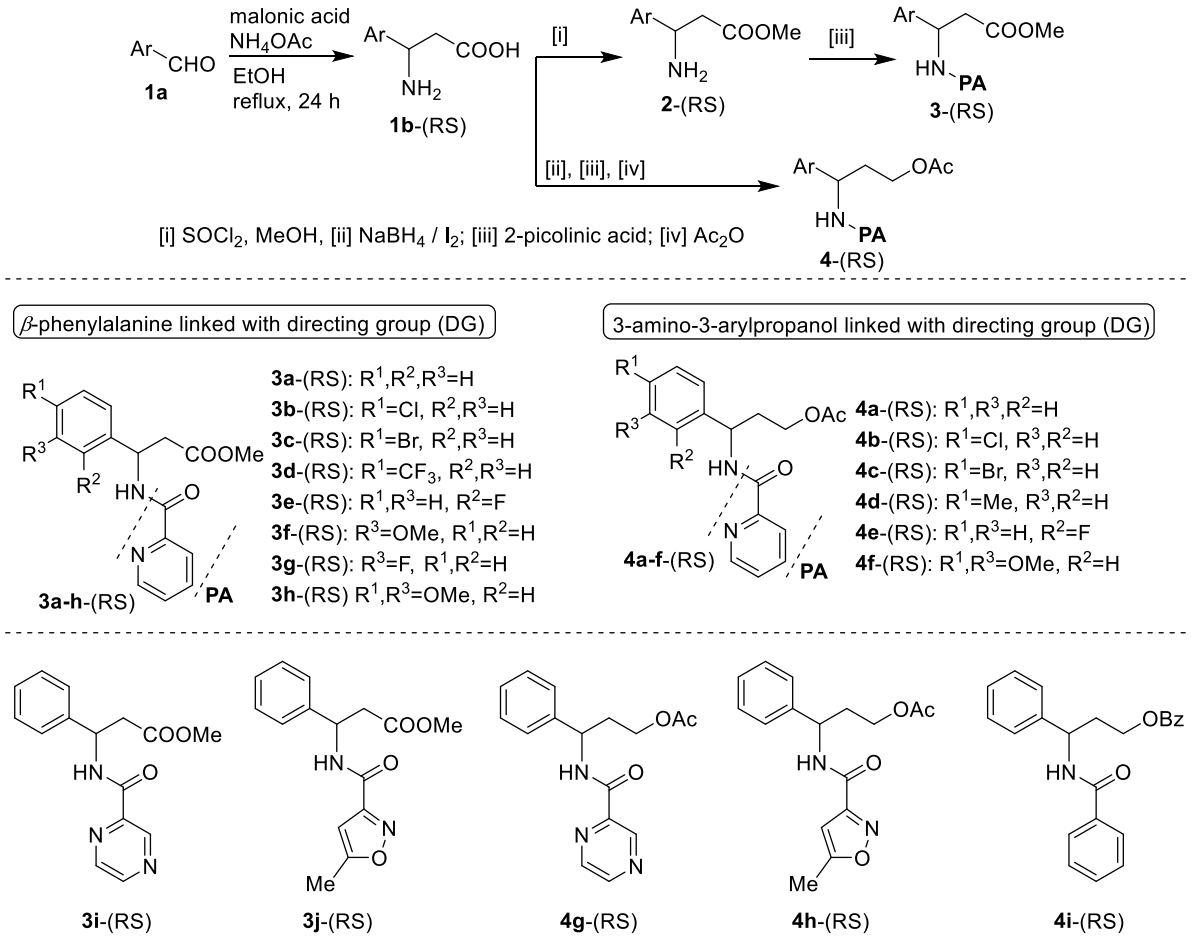
Apart from these reports to the best of our knowledge, the Pd-catalyzed C(sp^2)-H (*ortho*) functionalization of β-phenylalanines has not been explored. With our vested interest in the bidentate DG-aided C-H functionalization of amino acid derivatives, herein we report Pd(II)-catalyzed, picolinamide-directed C(sp^2)-H (*ortho*) arylation of β-phenylalanines and 3-amino-3-phenylpropanols scaffolds (Scheme 1c).

Theme of the work



Scheme 1c: General representation of C(sp^2)-H (*ortho*) arylation of *β*-phenylalanines and 3-amino-3-phenylpropanols scaffolds

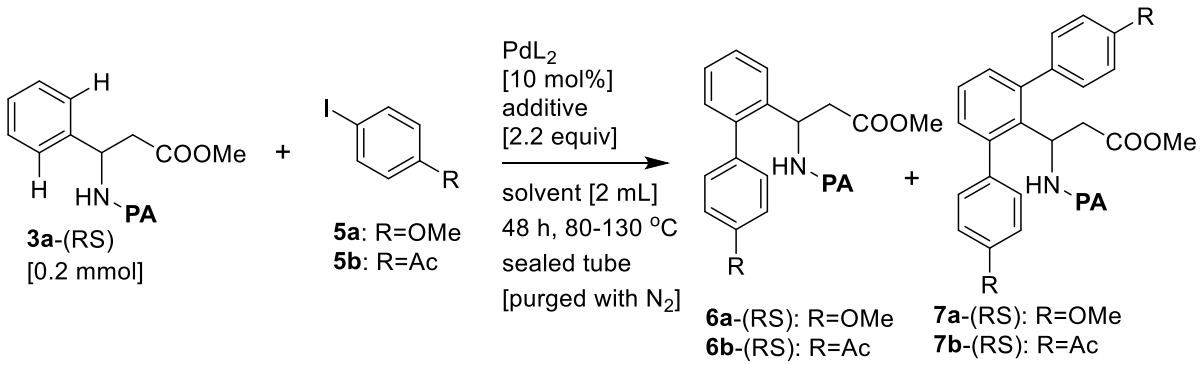
Result and discussion: To begin with our investigations on the construction of *ortho* C-H functionalized *β*-phenylalanine derivatives, initially, we prepared *β*-phenylalanine substrates possessing suitable DG (Scheme 2). Various *β*-phenylalanines **1b**-(RS) were assembled *via* the Rodionow's method.[20] Then, the corresponding *β*-phenylalanines **3**-(RS) possessing the picolinamide (PA) or other DGs were assembled from **1b**-(RS) *via* **2**-(RS). Next, the $NaBH_4$-mediated reduction of the carboxylic acid group in **1b**-(RS) gave the corresponding 3-amino-3-arylpropanols (*γ*-amino alcohols). Then, 3-amino-3-arylpropanols were used to assemble the corresponding 3-amino-3-arylpropanol substrates **4**-(RS) possessing the PA or other DGs using standard conditions.[7i] It may be noted that in *β*-phenylalanine substrates **3**-(RS), the C(sp^2)-H (*ortho*) bond is at the *δ*-position with respect to the carboxylic acid moiety and is at the *γ*-position with respect to the amino group linked with the DG. Similarly, in 3-amino-3-arylpropanol substrates **4**-(RS), the C(sp^2)-H (*ortho*) bond is at the *γ*-position with respect to the amino group linked with the DG.



Scheme 2: Substrates derived from *β*-phenylalanines and 3-amino-3-arylpropanols, which are used in the C(sp^2)-H functionalization reactions.

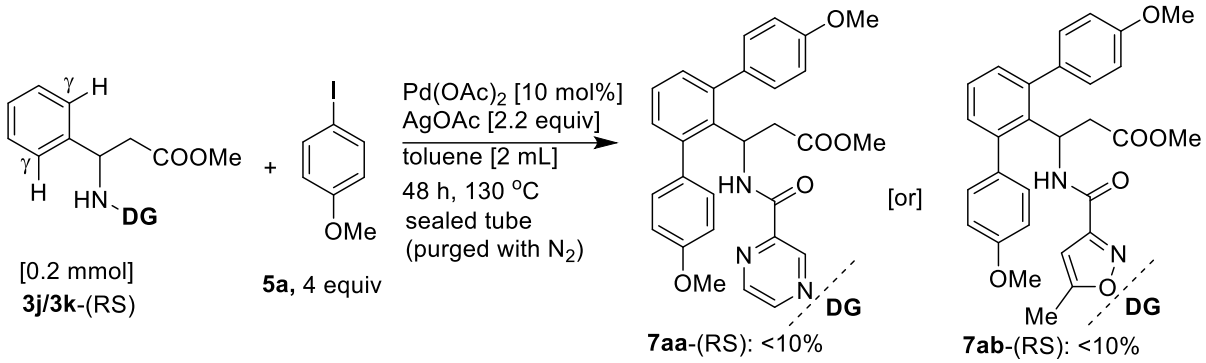
We then commenced the screening of reaction conditions for accomplishing the picolinamide DG-aided C(sp^2)-H (*ortho*) arylation of the *β*-phenylalanine substrate **3a**-(RS) with an aryl iodide **5a** using various palladium catalysts, additives, and solvents (Table 1). In general, under the bidentate directing group-aided Pd(II)-catalyzed C-H functionalization reactions, it is necessary to employ a halide ion scavenger as an additive.[3-9] Typically, a silver salt (e.g., AgOAc, Ag_2CO_3) or an alkali metal- based salt (e.g., K_2CO_3, KOAc) is used for this purpose. This additive helps to regenerate the Pd(II) catalyst in the proposed Pd^{II}-Pd^{IV} catalytic cycle[3-9] and promotes the C-H functionalization reaction. It is well known that the picolinamide DG-aided *γ*-C-H (*ortho*) functionalization is believed to undergo *via* a 5-membered palladacyclic transient species[3] in the proposed Pd^{II}-Pd^{IV} catalytic cycle.

Optimization table 1: Pd(II)-catalyzed picolinamide DG-aided C(sp^2)-H (*ortho*) arylation of *β*-phenylalanine substrate **3a**-(RS).



entry	PdL_2 [10 mol%]	5a/5b [equiv]	additives	solvent	T [ºC]	yield [%]	yield [%]
1	$Pd(OAc)_2$	5a [4]	AgOAc	toluene	110	6a-(RS):-	7a-(RS): 65
2	$Pd(OAc)_2$	5a [4]	AgOAc	*t*-amylOH	110	6a-(RS):-	7a-(RS): 60
3	$Pd(OAc)_2$	5a [4]	AgOAc	1,2-DCE	80	6a-(RS):-	7a-(RS): 55
4[a]	$Pd(OAc)_2$	5a [4]	Ag_2CO_3	*t*-amylOH	110	6a-(RS):-	7a-(RS): 56
5	$PdCl_2$	5a [4]	AgOAc	toluene	110	6a-(RS):-	7a-(RS): 70
6	$Pd(TFA)_2$	5a [4]	AgOAc	toluene	110	6a-(RS):-	7a-(RS): 30
7	$Pd(PPh_3)Cl_2$	5a [4]	AgOAc	toluene	110	6a-(RS):-	7a-(RS): 0
8[a]	$Pd(OAc)_2$	5a [4]	K_2CO_3	*p*-xylene	130	6a-(RS):-	7a-(RS): 25
9	**$Pd(OAc)_2$**	**5a [4]**	**AgOAc**	**toluene**	**130**	**6a-(RS):-**	**7a-(RS): 71**
10	$Pd(OAc)_2$	5a [1]	AgOAc	toluene	130	6a-(RS):-	7a-(RS): 40
11[b]	$Pd(OAc)_2$	5a [4]	AgOAc	toluene	130	6a-(RS):-	7a-(RS): 44
12	**$Pd(OAc)_2$**	**5b [4]**	**AgOAc**	**toluene**	**130**	**6b-(RS):**	**7b-(RS): 71**
13[b]	$Pd(OAc)_2$	5b [1.5]	AgOAc	toluene	110	6b-(RS): 24	7b-(RS): 20
14[b]	$Pd(OAc)_2$	5b [4]	AgOAc	toluene	110	6b-(RS): 15	7b-(RS): 53
15[b,d]	$Pd(OAc)_2$	5b [4]	AgOAc	toluene	100	6b-(RS): 10	7b-(RS): 28
16[b,d]	$Pd(OAc)_2$	5b [4]	AgOAc	toluene	90	6b-(RS): 19	7b-(RS): 25

[a] Additive = 2.5 equiv. [b] Reaction time = 24 h.
[c] The – [hyphen] symbol refers to the product not obtained.
[d] On a 0.1 mmol scale of **3a**-(RS).



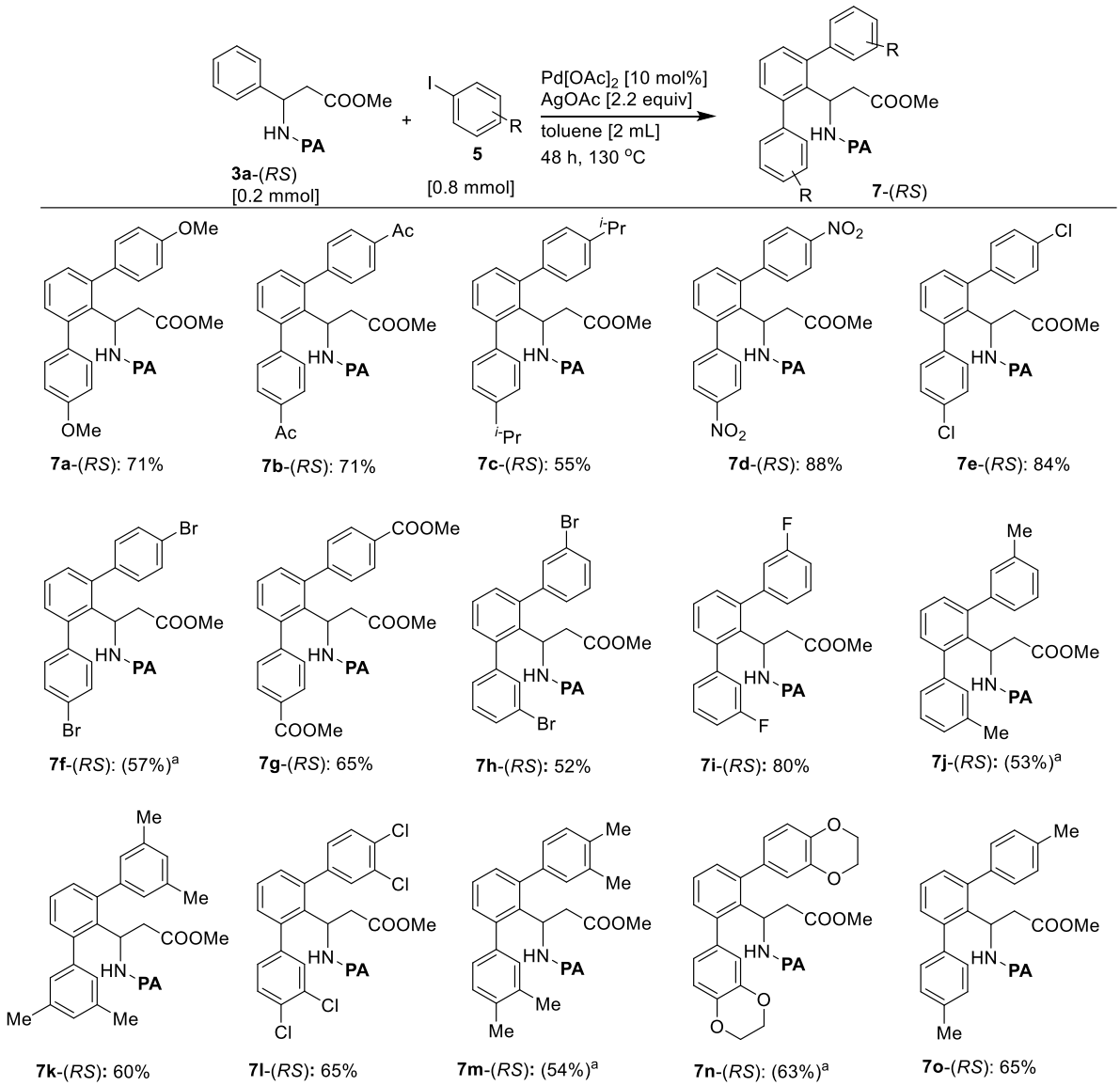
Scheme 3: Screening of different directing groups for (*ortho*)-arylation of *β*-phenylalanine

The *β*-phenylalanine substrate **3a**-(RS) was treated with *p*-anisyl iodide (**5a**) in the presence of the $Pd(OAc)_2$ catalyst (10 mol%) and AgOAc additive in toluene or *t*-AmylOH or 1,2-DCE at 80-110 °C for 48 h (under the conditions used by various groups including Daugulis, Chen, Jiang and our group).[3,7b,d,e,9a] These reactions yielded the bis C(sp^2)-H (*ortho*) arylated *β*-phenylalanine **7a**-(RS) (terphenyl type *β*-amino acid motif) in 55-65% yield (entries 1-3, Table 1). The $Pd(OAc)_2$-catalyzed *ortho* C-H arylation of **3a**-(RS) with **5a** using Ag_2CO_3 as an additive gave the product **7a**-(RS) in 56% yield (entry 4, Table 1). Then, heating **3a**-(RS) with **5a** in the presence of the $PdCl_2$ catalyst and AgOAc additive in toluene afforded the product **7a**-(RS) in 70% yield (entry 5, Table 1). The same reaction using $Pd(TFA)_2$ as the catalyst gave the product **7a**-(RS) in 30% yield and product **7a**-(RS) was not obtained using $Pd(PPh_3)_2Cl_2$ as the catalyst (entries 6 and 7, Table 1). Then, heating **3a**-(RS) with **5a** using K_2CO_3 as an additive in *p*-xylene at 130 °C gave the product **7a**-(RS) in 25% yield (entry 8, Table 1). We found out that the $Pd(OAc)_2$-catalyzed *ortho* C-H arylation of **3a**-(RS) with **5a** using AgOAc as an additive in toluene at 130 °C instead of 110 °C gave the product **7a**-(RS) in 71% yield (entry 9, Table 1). The column chromatographic purification of the corresponding crude mixtures of these reactions gave the bis C(sp^2)-H (*ortho*) arylated product **7a**-(RS) and the other expected mono C(sp^2)-H (*ortho*) arylated product **6a**-(RS) was not obtained in demonstrable amounts. As an observed trend in the literature, the usage of 3-4 equiv of aryl iodide is needed to get a good yield in the C-H arylation reactions.[3-9] Thus, the reaction condition of entry 9 comprising of the Pd(II)-catalyzed, picolinamide DG-aided C-H arylation of **3a**-(RS) with 4 equiv of **5a** is the suitable reaction condition for selectively obtaining **7a**-(RS).

Next, we aimed to obtain the mono *ortho* C(sp^2)-H arylated product **6a**-(RS) by using only an adequate amount of **5a**. We performed the Pd(II)-catalyzed C-H arylation of **3a**-(RS) with 1 equiv of **5a** (entry 10, Table 1). Nevertheless, this reaction afforded only **7a**-(RS) in 40% yield

and the mono C(sp^2)-H (*ortho*) arylated product **6a**-(RS) was not obtained in characterizable amounts. In another trial involving the Pd(II)-catalyzed reaction of **3a**-(RS) with **5a** in toluene at 130 ^oC for 24 h instead of 48 h was also afforded **7a**-(RS) in 44% yield and **6a**-(RS) was not obtained in characterizable amounts (entry 11, Table 1). We then continued to carry out further trials to assess the formation of the mono C(sp^2)-H (*ortho*) arylated product by using a different aryl iodide instead of **5a**. Heating **3a**-(RS) with 4-iodoacetophenone (**5b**, 4 equiv) under the conditions of entry 9 afforded only the bis C(sp^2)-H (*ortho*) arylated product **7b**-(RS) in 71% yield (entry12, Table 1). Heating **3a**-(RS) with 1.5 equiv of **5b** in the presence of the $Pd(OAc)_2$ catalyst and AgOAc additive in 110 ^oC for 24 h yielded both mono C(sp^2)-H arylated product **6b**-(RS) and bis C(sp^2)-H arylated product **7b**-(RS) in 24 and 20% yields, respectively (entry 13, Table 1). Furthermore, heating **3a**-(RS) with 4 equiv of **5b** in the presence of the $Pd(OAc)_2$ catalyst and AgOAc additive in toluene at 110 ^oC for 24 h instead of 48 h yielded both mono C(sp^2)-H arylated product **6b**-(RS) and bis C(sp^2)-H arylated product **7b**-(RS) in 15 and 53% yields, respectively (entry 14, Table 1). Treatment of **3a**-(RS) with 4 equiv of **5b** in toluene at 90 or 100 ^oC for 24 h gave the mono C(sp^2)-H arylated product **6b**-(RS) in 10-19% yield along with **7b**-(RS) in 25-28% yield (entries 15 and 16, Table 1). These attempts indicated that lowering the amount of aryl iodide to 1.5 equiv or performing the reaction at 90-110 ^oC for 24 h would afford the mono C(sp^2)-H arylated product **6b**-(RS) but in demonstrable yield along with **7b**-(RS). Next, we performed the Pd(II)-catalyzed C-H arylation of substrates **3i**-(RS) and **3j**-(RS) possessing other DGs such as pyrazine-2-carboxamide or 5-methylisoxazole-3-carboxamide with **5a**, which gave the corresponding products **7aa**-(RS) and **7ab**-(RS) in poor yields (<10%) (Scheme 3). Accordingly, picolinamide was found to be the effective directing group for accomplishing the C(sp^2)-H (*ortho*) arylation of **3a**-(RS).

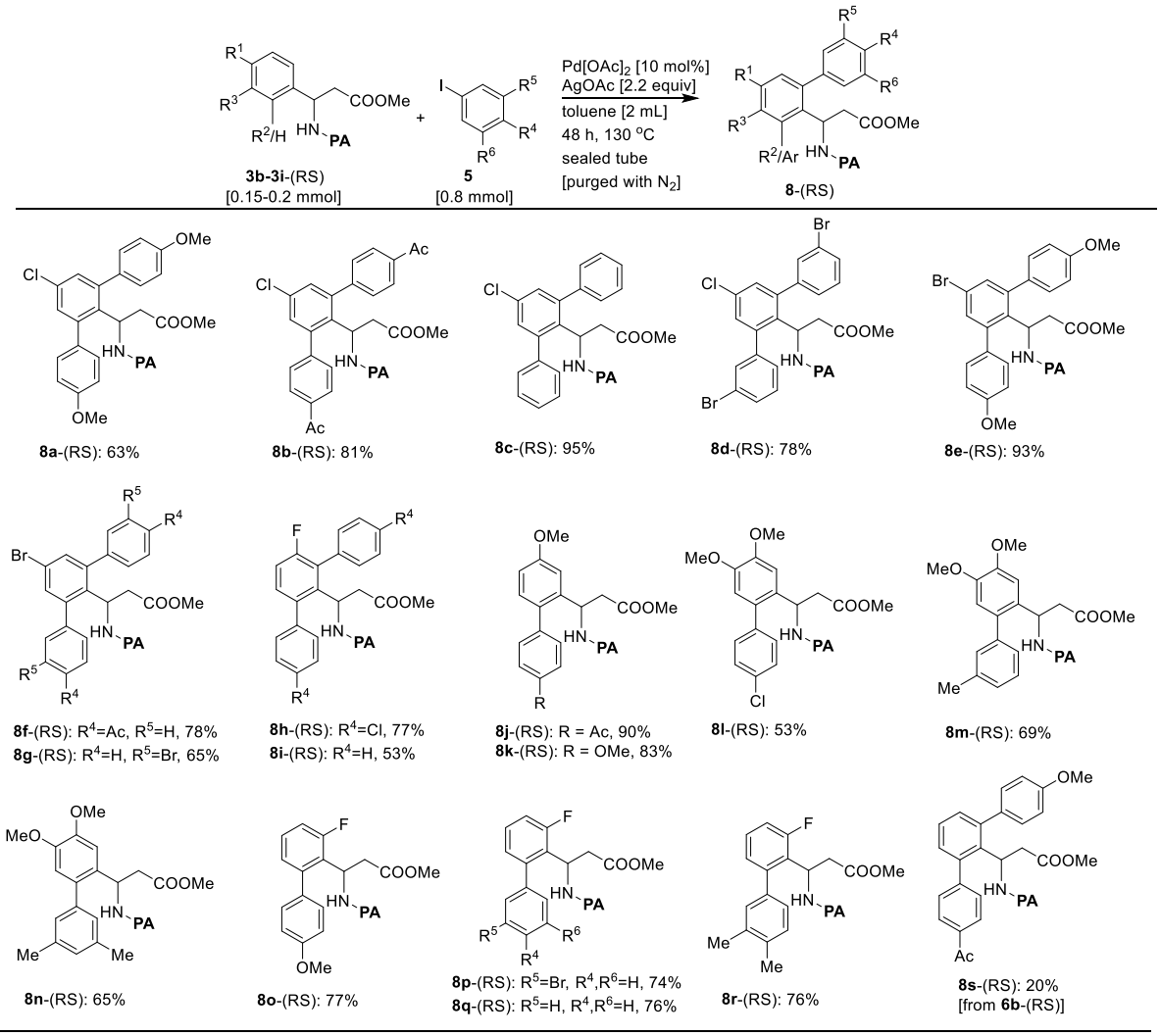
After performing the screening of conditions, we aimed to expand the substrate scope and generality of this protocol comprising *ortho* C-H functionalization of *β*-phenylalanines. Initially, we performed the Pd(II)-catalyzed, picolinamide-directed C(sp^2)-H arylation of *β*-phenylalanine **3a**-(RS) with a variety of aryl iodides (Scheme 4a, 4b). Heating *β*-phenylalanine **3a**-(RS) with aryl iodides containing a substituent at the *para* position in the presence of the



[a] 0.25 mmol scale.

Scheme 4a: Substrate scope investigation. Pd(II)-catalyzed C-H arylation of the *β*-phenylalanine.

$Pd(OAc)_2$ catalyst and AgOAc additive in toluene at 130 °C afforded the corresponding bis C(sp^2)-H (*ortho*) arylated products (terphenyl-based *β*-phenylalanines) **7a-g**-(RS) and **7o**-(RS) in 55-88% yields. Similarly, the Pd(II)-catalyzed C-H arylation of **3a**-(RS) with aryl iodides containing a substituent at the *meta* position afforded the corresponding bis C(sp^2)-H (*ortho*) arylated *β*-phenylalanines **7h-j**-(RS) in 52-80% yields. Subsequently, the Pd(II)-catalyzed C-H arylation of **3a**-(RS) with disubstituted aryl iodides afforded the corresponding products **7k-n**-(RS) in 54-65% yields (Scheme 4a).

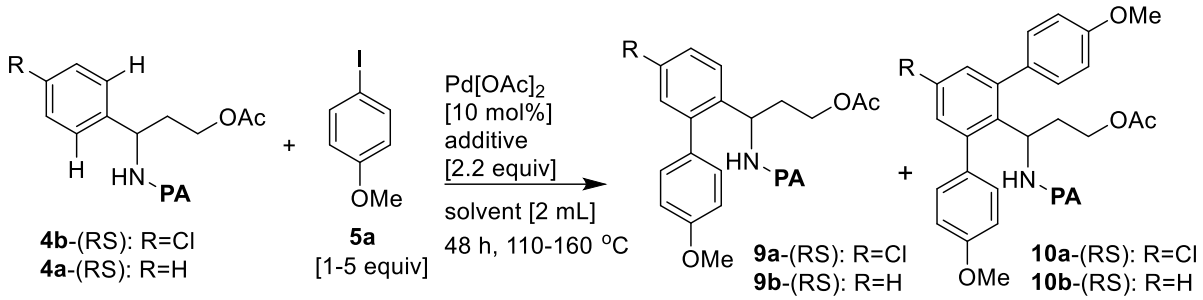


Scheme 4b: Substrate scope investigation. Pd(II)-catalyzed C-H arylation of the *β*-phenylalanine containing substituent at phenyl ring.

We then performed the Pd(II)-catalyzed, C(sp^2)-H (ortho) arylation of *β*-phenylalanine substrates possessing substituents in the aryl ring. The *β*-phenylalanine substrates 3b-(RS) or 3c-(RS) possessing a substituent (e.g., Cl and Br) at the para position with various aryl iodides containing a substituent at the meta or para position were reacted in the presence of the $Pd(OAc)_2$ catalyst and AgOAc additive in toluene at 130 °C for 48 h. These reactions gave the corresponding bis C(sp^2)-H (ortho) arylated products (terphenyl-based *β*-phenylalanine derivatives) 8a-g-(RS) in 63-95% yields (Scheme 4b). The Pd(II)-catalyzed C-H arylation of the *β*-phenylalanine substrate 3h-(RS) containing a fluorine substituent at the meta position with aryl iodides yielded the corresponding bis C(sp^2)-H (ortho) arylated *β*-phenylalanines 8h,i-(RS) in 53-77% yields. Being a small group the fluorine substituent in *β*-phenylalanine substrate 3h-(RS) did not

provide any hindrance for the C-H arylation of the C(sp^2)-H (ortho) bond present next to it. On the other hand, the Pd(II)-catalyzed C-H arylation of the meta methoxy *β*-phenylalanine substrate 3g-(RS) with aryl iodides provided the corresponding mono C(sp^2)-H (*ortho*) arylated products (biaryl-based *β*-phenylalanines) 8j,k-(RS) in 83-90% yields. These results indicated that the C-H arylation in the meta-methoxy *β*-phenylalanine substrate 3g-(RS) has occurred only at the less hindered C(sp^2)-H (*ortho*) bond. Subsequently, the Pd(II)-catalyzed C-H arylation of dimethoxy *β*-phenylalanine substrate 3i-(RS) with aryl iodides provided the corresponding mono C(sp^2)-H (ortho) arylated products 8l-n-(RS) in 53-69% yields. Furthermore, the Pd(II)-catalyzed C-H arylation of *β*-phenylalanine substrate 3f-(RS) containing a fluorine substituent at the ortho position with aryl iodides provided the corresponding biaryl-based *β*-phenylalanine derivatives 8o-r-(RS) in 74-77% yields (Scheme 3b). Along this line, the Pd(II)-catalyzed C-H arylation of mono C(sp^2)-H (ortho) arylated product 6b-(RS) with 5a provided the terphenyl *β*-phenylalanine derivative 8s-(RS) in a demonstrable yield (20%) (Scheme 4b).

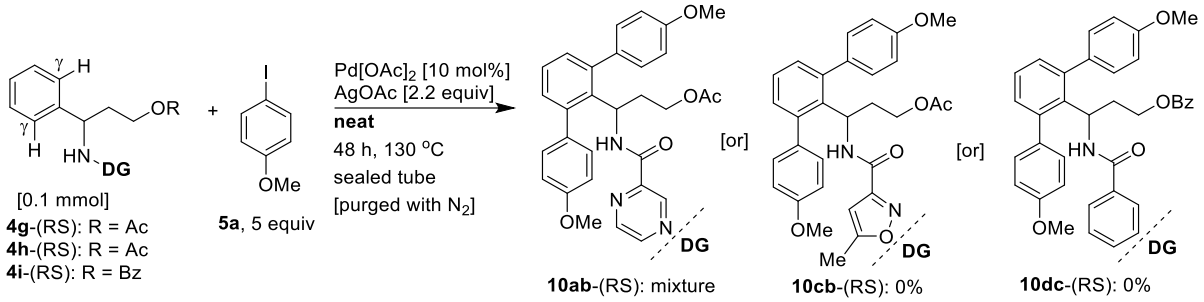
Optimization table 2: Pd(II)-catalyzed picolinamide-aided C(sp^2)-H (*ortho*) arylation of 3-amino-3-phenylpropanol substrate **4b**-(RS) / **4a**-(RS).



entry	4a/4b-(*RS*) (0.2 mmol)	5a [equiv]	additives	solvent	T [ºC]	9a/9b-(*RS*) yield [%]	10a/10b-(*RS*) yield [%]
1[a]	4b-(RS)	4	AgOAc	toluene	110	-	10a-(RS): 40
2[a]	4b-(RS)	4	AgOAc	*p*-xylene	130	-	10a-(RS): 60
3[a,d]	4b-(RS)	4	AgOAc	toluene	110	-	10a-(RS): 37
4[a,d,e]	4b-(RS)	4	AgOAc	*p*-xylene	130	-	10a-(RS): 37
5[b]	4b-(RS)	4	AgOAc	*p*-xylene	160	-	10a-(RS): 43
6[a]	4b-(RS)	4	Ag_2CO_3	1,4-Dioxane	101	-	10a-(RS): -
7[b]	4b-(RS)	4	AgOAc	HFIP	110	-	10a-(RS): -

8[a]	4b-(RS)	4	AgOAc	*t*-AmylOH	102	-	10a-(RS): -
9[a,f]	4b-(RS)	4	AgTFA	toluene	110	-	10a-(RS): -
10[b]	4b-(RS)	5	AgOAc	neat	130	-	10a-(RS): 41
11[b]	4b-(RS)	5	Ag_2CO_3	neat	130	-	10a-(RS): 41
12[b]	4a-(RS)	4	AgOAc	*p*-xylene	130	-	10b-(RS):55
13[b]	**4a-(RS)**	**5**	**AgOAc**	**neat**	**130**	**-**	**10b-(RS): 64**
14[b]	4b-(RS)	1	AgOAc	neat	130	-	10a-(RS): 19
15[b]	4a-(RS)	1	AgOAc	neat	130	-	10b-(RS): 7

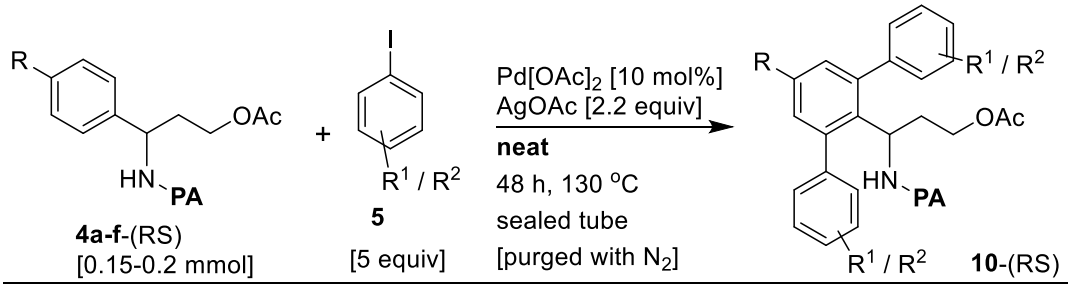
[a] Reaction was done in RB flask [under a nitrogen atm]. [b] Reaction was done in a sealed tube [purged with a nitrogen atm]. [c] The – [hyphen] symbol refers to the product not obtained. [d] $(BnO)_2PO_2H$ [0.2 equiv] was used as an additional additive. [e] 5 mol% of $Pd(OAc)_2$ was used. [f] $Pd(TFA)_2$ was used instead of $Pd(OAc)_2$.

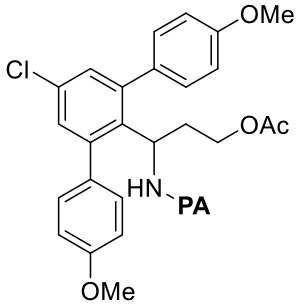


Scheme 5: Screening of different directing groups for (*ortho*)-arylation of 3-amino-3-phenylpropanol

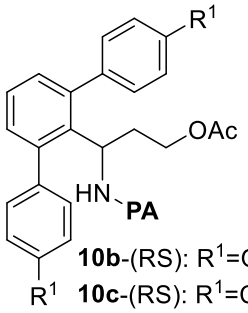
Successively, we wished to establish the C(sp^2)-H (*ortho*) arylation of 3-amino-3-phenylpropanols (*γ*-amino alcohols) which can be derived from *β*-phenylalanines. We recently reported a few *ortho* C-H oxygenation reactions using 3-amino-3-phenylpropanol substrates **4a-e**-(RS).[7i] We wished to obtain suitable reaction conditions for accomplishing the *ortho* C-H arylation of 3-amino-3-phenylpropanol substrate **4b**-(RS) with aryl iodide **5a** in the presence of palladium catalysts, additives and solvents. Heating **4b**-(RS) and **5a** (4 equiv) in the presence of $Pd(OAc)_2$ catalyst and AgOAc additive in toluene or *p*-xylene (at 110-130 °C) gave the bis C(sp^2)-H (*ortho*) arylated product (terphenyl-based *γ*-amino alcohol motif) **10a**-(RS) in 40-60% yields (entries 1 and 2, Table 2). The same reactions were performed using $(BnO)_2PO_2H$[5n] as an additional additive $(BnO)_2PO_2H$ is believed to improve the yield of C-H functionalized product). These trials did not provide **10a**-(RS) with improved yield and **10a**-(RS) was obtained in 37% yield (entries 3 and 4, Table 2).

Heating **4b**-(RS) and **5a** in the presence of $Pd(OAc)_2$ and AgOAc in *p*-xylene at a high temperature of 160 ^oC provided **10a**-(RS) in slightly improved yield of 43% (entry 5, Table 2). Then, the C-H arylation of **4b**-(RS) with **5a** was attempted in solvents such as 1,2-dioxane or HFIP or *t*-AmylOH and these trials did not provide **10a**-(RS) (entries 6-8, Table 2). The C-H arylation of **4b**-(RS) with **5a** using $Pd(TFA)_2$ and AgTFA additive did not provide **10a**-(RS) (entry 9, Table 2). Next, we tried the C-H arylation of **4b**-(RS) with **5a** (5 equiv) using the $Pd(OAc)_2$ catalyst and AgOAc or Ag_2CO_3 additive in neat condition at 130 ^oC and these reactions afforded the product **10a**-(RS) in 41% yield (entries 10 and 11, Table 2). We did not obtain the other expected mono *ortho* arylated product **9a**-(RS) in any of these trials. To find out whether we can obtain the mono arylated product, we also tried the C-H arylation of another substrate **4a**-(RS) with **5a** using the $Pd(OAc)_2$ catalyst and AgOAc additive in *p*-xylene at 130 ^oC. This reaction gave the bis γ-C(sp^2)-H (*ortho*) arylated product **10b**-(RS) in 55% yield (entry 12, Table 2). Then, the C-H arylation of **4a**-(RS) with 5 equiv of **5a** using the $Pd(OAc)_2$ catalyst and AgOAc additive in neat condition at 130 ^oC provided the product **10b**-(RS) in 64% yield (entry 13, Table 2). These trials also did not provide the mono *ortho* arylated product **9b**-(RS). Furthermore, we also attempted the Pd(II)-catalyzed C-H arylation of **4b**-(RS) or **4a**-(RS) with 1 equiv of **5a**. These reactions afforded the corresponding products **10a**-(RS) or **10b**-(RS) in 7-19% yields. The corresponding mono γ-C(sp^2)-H (*ortho*) arylated products **9b**-(RS) or **9b**-(RS) were not obtained (entries 14 and 15, Table 2). It is a general trend that the *ortho* C-H arylation of aryl ring possessing two equivalent *ortho* C-H bonds provided the bis *ortho* C-H arylated products. Selective formation of mono *ortho* C-H arylated product is rarely observed.[3,5,7,9] The Pd(II)-catalyzed C-H arylation of substrates **4g-i**-(RS) possessing other directing groups with **5a** were not fruitful (Table 2). These reactions indicated that picolinamide DG provided the required assistance for the *ortho* C-H functionalization when compared to other DGs of corresponding substrates **4g-i**-(RS) [3,5,7,9] (Scheme 5).

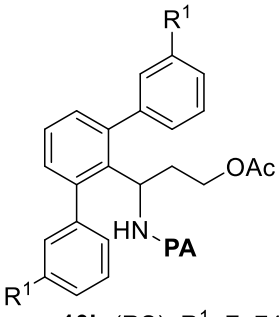




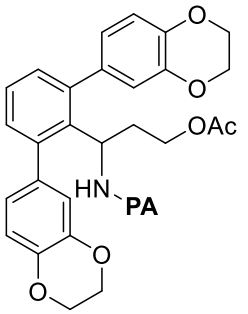
10a-(RS): 60%[a]
10a-(RS): 41%



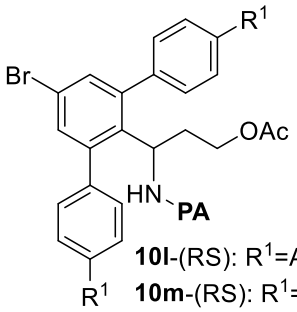
10b-(RS): R^1=OMe, 64%
10c-(RS): R^1=Cl, 64%
10d-(RS): R^1=CF_3, 83%
10e-(RS): R^1=H, 63%
10f-(RS): R^1=Me, 70%
10g-(RS): R^1=*t*-Bu, 57%



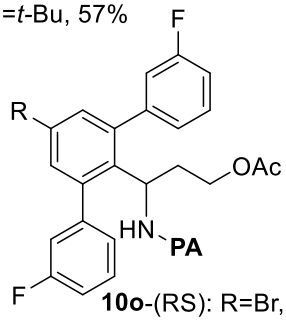
10h-(RS): R^1=F, 74%
10i-(RS): R^1=Br, 56%
10j-(RS): R^1=Cl, 53%



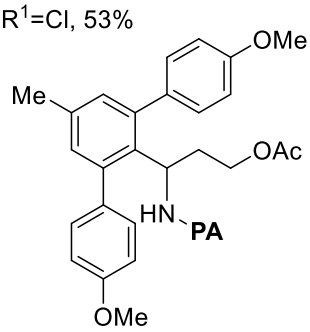
10k-(RS): 71%



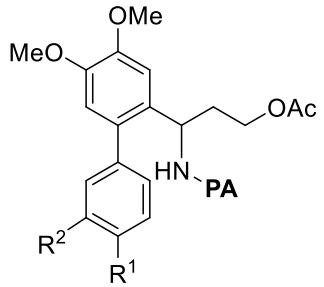
10l-(RS): R^1=Ac, 56%
10m-(RS): R^1=Me, 57%
10n-(RS): R^1=COOEt, 34%



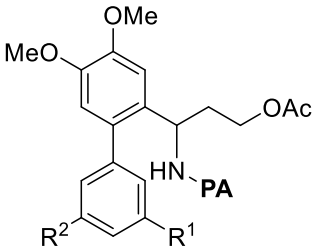
10o-(RS): R=Br, 68%
10p-(RS): R=Cl, 58%



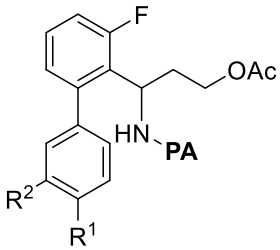
10q-(RS): R=Me, 47%



10s-(RS): R^1=H, R^2=H, 69%
10t-(RS): R^1=Ac, R^2=H, 70%
10u-(RS): R^1=OMe, R^2=H, 76%
10v-(RS): R^1=Me, R^2=H, 56%
10w-(RS): R^1=Cl, R^2=Cl, 61%



10x-(RS): R^1= H, R^2= Br, 74%
10y-(RS): R^1= H, R^2= F, 51%
10z-(RS): R^1= Me, R^2= Me, 59%



10r-(RS): R^1= Ac, R^2= H, 58%
10aa-(RS): R^1= H, R^2= Br, 60%

[a] Reaction was performed in *p*-xylene solvent in RB flask.

Scheme 6: Substrate scope investigation. Pd(II)-catalyzed C(sp^2)-H (*ortho*) arylation of 3-amino-3-phenylpropanols (*γ*-amino alcohols).

Having done the screening of reaction conditions, we wished to expand the substrate scope. We then performed the Pd(II)-catalyzed, AgOAc-promoted picolinamide-directed *ortho* C-H arylation of 3-amino-3-phenylpropanol substrates **4a-f**-(RS) with a variety of aryl iodides (Scheme 6). The 3-amino-3-phenylpropanol substrate **4a**-(RS) and **4b-d**-(RS) possessing a substituent (e.g., Cl, Br and Me) at the *para* position with *meta* or *para* substituted aryl iodides or disubstituted aryl iodide were reacted in the presence of $Pd(OAc)_2$ and AgOAc in neat condition at 130 ^oC for 48 h. These reactions yielded the corresponding bis C(sp^2)-H (*ortho*) arylated products (terphenyl-based *γ*-amino alcohol derivatives) **10a-q**-(RS) in 34-83% yields. Then, *meta* and *para* dimethoxy substituted 3-amino-3-phenylpropanol substrate **4f**-(RS) and substrate **4e**-(RS) containing a fluorine substituent at the *ortho* position were subjected to the Pd(II)-catalyzed *ortho* C-H arylation conditions. These trials afforded the corresponding mono arylated products (biaryl-based *γ*-amino alcohol derivatives) **10r-z**-(RS) and **10aa**-(RS) in 51-76% yields. The *ortho* C-H arylation in the *meta* and *para* dimethoxy substituted substrate **4f**-(RS) has occurred only at the less hindered C(sp^2)-H (*ortho*) bond. In general, this is an observed trend that aromatic carboxamides possessing a substituent at the *meta* position were found to yield the mono arylated products.[3,7b,9b]

The mechanism of bidentate directing group-aided, chelation-assisted, site-selective C-H activation and functionalization reaction is well known.[3,4,5a] Along this, the proposed mechanism of the Pd(II)-catalyzed, picolinamide DG-aided C(sp^2)-H (*ortho*) functionalization of benzylamine type substrates involving a Pd^{II}-Pd^{IV} catalytic cycle is documented.[3,4,6-9] Accordingly, the intermolecular C(sp^2)-H (*ortho*) functionalization of *β*-phenylalanines discussed in this work is believed to undergone *via* the 5-membered transient palladacycle in the well-documented Pd^{II}-Pd^{IV} catalytic cycle.[3,4,6-9]

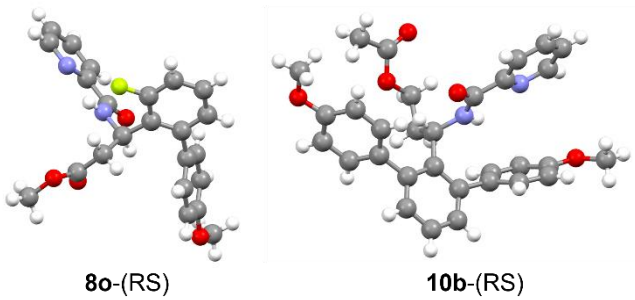
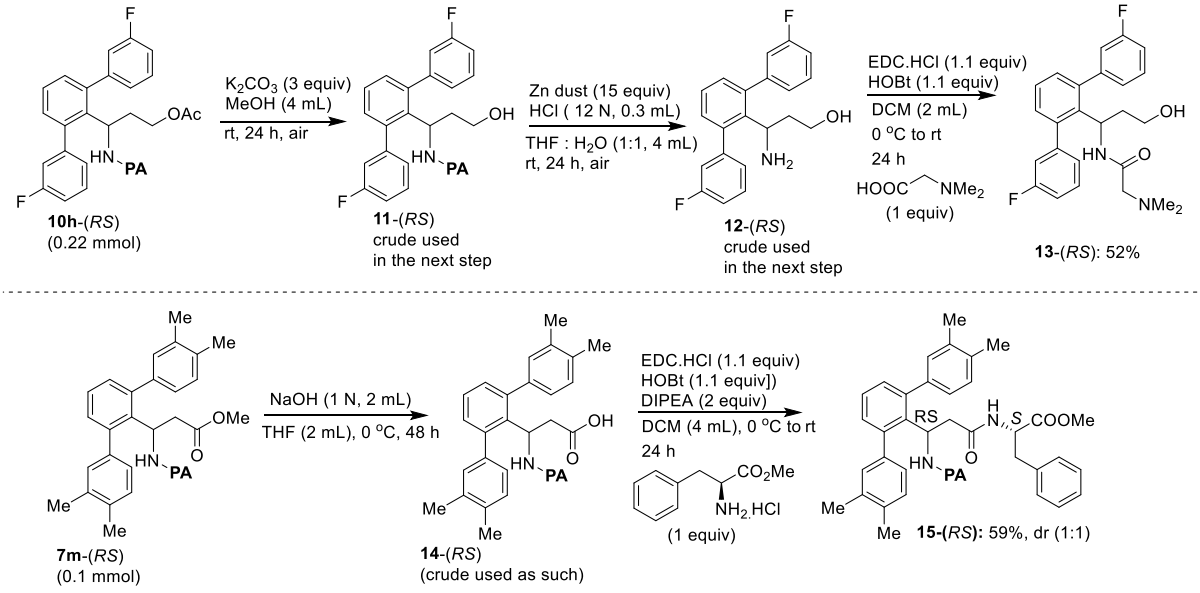


Figure 2 The X-ray structures (ball and stick model) of *ortho* C-H arylated *β*-phenylalanine **8o**-(RS) and 3-amino-3-phenylpropanol **10b**-(RS).

Additionally, the X-ray structure analysis of representative mono C(sp^2)-H (*ortho*) arylated *β*-phenylalanine **8o**-(RS) and bis C(sp^2)-H (*ortho*) arylated 3-amino-3-phenylpropanol **10b**-(RS) derivatives were obtained (Figure 2).[23] These X-ray structures corroborated the occurrence of the Pd(II)-catalyzed picolinamide-aided arylation at the *ortho* C(sp^2)-H bond in *β*-phenylalanine substrate **3f**-(RS) and 3-amino-3-phenylpropanol substrate **4a**-(RS), respectively.

Subsequently, we tried the removal of picolinamide DG (picolinoyl moiety) from the *ortho* C-H arylated *β*-phenylalanine derivatives. The compound **10h**-(RS) was subjected to the deacetylation of the OAc group to afford **11**-(RS) possessing the picolinamide DG, which was then treated with Zn dust/12 N HCl in THF/H_2O at rt for 24 h.[24] This process gave the picolinamide directing group-free terphenyl-based *γ*-amino alcohol **12**-(RS). Subsequently, the crude sample **12**-(RS) was subjected to the amide coupling reaction with *N*,*N*-dimethyl glycine. Accordingly, the terphenyl-based *γ*-amino alcohol-glycine coupled product **13**-(RS) was obtained in 52% yield (Scheme 7). Additionally, we wished to prepare a dipeptide molecule using the *ortho* C-H functionalized *β*-phenylalanine (*β*-amino acid) derivatives (Scheme 7). Then, the *ortho* C-H arylated *β*-phenylalanine **7m**-(RS) was subjected to the ester hydrolysis to afford its *β*-amino acid derivative, which was treated with L-phenylalanine methyl ester to afford the dipeptides **15**-(RS) (*dr* ~1:1) (Scheme 7).



Scheme 7: Directing group removal and Peptide formation.

In summary, we have shown the Pd(II)-catalyzed, site-selective C(sp^2)-H (*ortho*) arylation of *β*-phenylalanines and 3-amino-3-phenylpropanols to obtain various unnatural *β*-phenylalanine

(*β*-amino acid) and 3-amino-3-phenylpropanol derivatives. The C(sp^2)-H (*ortho*) arylation reactions gave biaryl-or terphenyl-based *β*-phenylalanine (*β*-amino acid) motifs. The C(sp^2)-H (*ortho*) arylation of 3-amino-3-phenylpropanols (*γ*-amino alcohols) has led to the assembling of terphenyl-based *γ*-amino alcohols. We have also shown representative synthetic transformations using terphenyl-based *β*-phenylalanines, *γ*-amino alcohols and performed the synthesis of a few dipeptide molecules using *ortho* C-H functionalized *β*-phenylalanines. Compounds have been characterized by NMR, HRMS, and X-ray structure analysis.[23] *β*-Phenylalanine is an important *β*-amino acid motif in chemical biology and medicinal chemistry. Accordingly, this paper revealed the expansion of the library of *β*-phenylalanine (*β*-amino acid) derivatives through the site-selective C-H functionalization and its application in the synthesis of biaryl-or terphenyl-type amino acid derivatives[4,25,26] Additionally, this work contributes to the substrate scope development in the bidentate directing group-aided C-H activation and functionalization method.

General. Reactions were done in oven-dried round-bottom flasks/sealed tubes/ pressure tubes in anhydrous solvent/neat condition under a nitrogen/air atm (see the respective Table/Scheme/procedure for specific details). TLC analysis was performed on silica gel or silica gel 60 F_{254} pre-coated plates and components was visualized with exposure to iodine vapour or by irradiation under a UV lamp. The column chromatography purification was performed using silica gel (100-200 mesh) or neutral alumina (eluent = ethyl acetate:hexanes). ^{1}H NMR and ^{13}C{^{1}H} NMR spectra of samples have been recorded on 400 and ~101 (or) 300 and ~75 (or) 500 and ~126 MHz spectrometers, respectively (using TMS as an internal standard). In some of the ^{1}H and ^{13}C{^{1}H} NMR spectra of some samples, we observed the broadening of some signals (aromatic signals). The HRMS data were obtained from QTOF mass analyser using electrospray ionization (ESI) method. The IR spectra of samples have been recorded using KBr pellets or in an appropriate solvent. Standard procedures reported by various groups including our group were adapted to link the directing groups and perform the C-H arylation reactions conditions. For some biaryl or terphenyl compounds containing fluorine atoms, in ^{19}F{^{1}H} NMR 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). Substrates **4a-e**-(RS) were known compounds (ref. Y. Aggarwal, R. Padmavathi, P. Singh, S. A. Babu, *Asian J. Org. Chem.* **2022**, *11*, e202200327).

Procedure for the preparation of *β*-phenylalanine (Procedure A): To a solution of malonic acid (2 equiv) and benzaldehyde (10 mmol) in dry ethanol (20 mL), ammonium acetate (2 equiv) was added. The reaction mixture was refluxed for 24 h under a nitrogen atm and cooled to rt. Then, the resulting precipitate was filtered off, washed with cold ethanol, and dried in a vacuum to give *β*-phenylalanine (3-amino-3-arylpropanoic acid).(*via* the Rodionow's method, a) W. M. Rodionow, *J. Am. Chem. Soc.* **1929**, *51*, 847-852; b) W. M. Rodionow, E. A. Postovskaja, *J. Am. Chem. Soc.* **1929**, *51*, 841-847; c) J. I. Grayson, J. Roos, S. Osswald, *Org. Process Res. Dev.* **2011**, *15*, 1201- 1206).

Procedure for the esterification of *β*-phenylalanine and preparation of *β*-phenylalanine ester (Procedure B): To a solution of *β*-phenylalanine (1 mmol) in dry MeOH in a RB flask fitted with a condenser with a calcium chloride guard tube on it and thionyl chloride (2 equiv) was added at 0 ^{o}C under a nitrogen atm. The resulting reaction mixture was stirred at 60 ^{o}C for 12 h. Then, the resulting solution was concentrated to give the *β*-phenylalanine methyl ester (see the respective Table/Scheme for specific entry).

Procedure for the synthesis of *γ*-amino alcohol from *β*-phenylalanine (Procedure C): A suspension of *β*-phenylalanine (10 mmol) and $NaBH_4$ (2.5 equiv) in dry THF (20 mL) was cooled at 0 °C under an argon atm. To this solution, a solution of I_2 (1.2 equiv) in dry THF was added. The reaction mixture was refluxed for 24 h and then cooled to rt. Methanol was added dropwise until the solution became clear. The solution was stirred at rt for 1 h and the solvent was removed under reduced pressure. To the residue was added 20% aqueous KOH (30 mL) and the mixture was stirred at rt for 4 h. The aq. phase was extracted with DCM and washed with water. The combined organic layers were dried over anhydrous sodium sulphate and evaporated under a reduced pressure to give the *γ*-amino alcohol, which was used in procedure D (see the respective Table/Scheme for specific entry).

Procedure linking a directing group with the amino group of *β*-phenylalanine methyl ester / *γ*-amino alcohol (Procedure D): An appropriate amount of carboxylic acid (directing group) (1-10 mmol), *N,N'*-dicyclohexylcarbodiimide (1.1 equiv), 1-hydroxybenzotriazole hydrate (1.1 equiv) in DCM (2-20 mL) were stirred at 0 ^{o}C for 1 h under a nitrogen atm. Then an appropriate amount of *β*-phenylalanine methyl ester / *γ*-amino alcohol (1 equiv) was added to the above mixture and stirred for 24 h at rt. Then, the resulting solution was subjected to an aq. workup and washed with aq. sodium bicarbonate solution. Then, the resulting crude reaction mixture was purified using silica gel column chromatography to obtain corresponding *β*- phenylalanine methyl ester/ *γ*-amino alcohol carboxamide (linked with a directing group at the amino group) (see the respective Table/Scheme for specific entry).

Procedure for the acetylation of free alcohol group in *γ*-amino alcohol carboxamide (linked with a directing group) (Procedure E): An appropriate amount of *γ*-amino alcohol carboxamide (linked with a directing group and having the free OH group), was dissolved in dry DMF followed by the addition of 4-(dimethylamino)pyridine (0.1 equiv) and acetic anhydride (1.1 equiv) and the resulting reaction mixture was stirred at rt for 12 h under a nitrogen atm. Then, the resulting solution was diluted with water and extracted with EtOAc, and the combined organic phase was washed with brine solution. The resulting solution was then concentrated and purified on silica gel column chromatography (eluent = EtOAc:hexanes) to give the corresponding OH group acetylated *γ*-amino alcohol carboxamide (linked with a directing group) (see the respective Table/Scheme for specific entry).

Procedure for the Pd(II)-catalyzed *ortho* C-H arylation of *β*-phenylalanine methyl ester carboxamide (Procedure F): A mixture of *β*-phenylalanine ester carboxamide possessing a directing group (1 equiv), aryl iodide (4 equiv), $Pd(OAc)_2$ (10 mol%) and AgOAc (2.2 equiv) in dry toluene (2 mL) was heated in a sealed tube purged with a nitrogen atm at 130 ^oC for 48 h. After the reaction period, the reaction mixture was concentrated in a vacuum and purification of the resulting reaction mixture by column chromatography on silica gel (eluent = EtOAc:hexanes) gave the corresponding *ortho* C-H arylated *β*-phenylalanine ester carboxamide (see the respective Table/Scheme for specific entry).

Procedure for the Pd(II)-catalyzed *ortho* C-H arylation of *γ*-amino alcohol carboxamide (Procedure G): A mixture of *γ*-amino alcohol carboxamide (1 equiv), aryl iodide (5 equiv), $Pd(OAc)_2$ (10 mol%) and AgOAc (2.2 equiv) were added in a pressure tube/sealed tube capped with silicone septum and tube was purged with nitrogen atm and then the reaction mixture was heated at 130 ^oC for 48 h. After the reaction period, purification of the resulting reaction mixture by column chromatography on silica gel (eluent = EtOAc:hexanes) gave the corresponding *ortho* C-H arylated *γ*-amino alcohol carboxamide (see the respective Table/Scheme for specific entry).

Procedure for the deacetylation of (OAc group) in *ortho* C-H arylated *γ*-amino alcohol carboxamide (Procedure H): An *ortho* C-H arylated *γ*-amino alcohol carboxamide (possessing the OAc group) (1 equiv) was dissolved in MeOH (4 mL) in a RB flask. To this solution, K_2CO_3 (3 equiv) was added, and the reaction mixture was stirred for 24 h in the open air. After the reaction was over, the reaction mixture was concentrated in a vacuum and then diluted with ethyl acetate and washed with sodium bicarbonate solution and this resulting solution was dried over anhydrous sodium sulphate. The resulting solution was then concentrated and used for the next step without further purification (see the respective

Table/Scheme for specific entry).

Procedure for the removal of picolinoyl group from the *ortho* C-H arylated *γ*-amino alcohol linked with picolinamide directing group (Procedure I): In a RB flask, an appropriate amount of *ortho* C-H arylated *γ*-amino alcohol linked with picolinamide (1 equiv), zinc dust (15 equiv), 12 N HCl (0.3 mL) and THF:H_2O (1:1, 4 mL) were added. The reaction mixture was stirred at rt for 24 h under the open air. After the reaction period, the reaction was filtered through a celite plug. The filtrate was transferred into a separating funnel with 2 M NaOH (50 mL) and extracted with DCM. The reaction mixture was concentrated in a vacuum, and we then used it in the next step (see the respective Table/Scheme for specific entry).

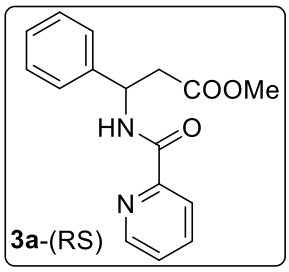
Procedure for the coupling of *N,N*-dimethyl glycine with *ortho* C-H arylated *γ*-amino alcohol (Procedure J): An appropriate amount of *N,N*-dimethyl glycine (1 equiv), *N,N'*-dicyclohexylcarbodiimide (1.1 equiv), 1-hydroxybenzotriazole hydrate (1.1 equiv) in DCM (2-4 mL) were stirred for 1 h at 0 ^oC under a nitrogen atm. Then, an appropriate *ortho* C-H arylated *γ*-amino alcohol substrate (1 equiv) was added to the above mixture and stirred for 24 h at rt. Then, the resulting solution was subjected to an aq. workup and washed with aq. sodium bicarbonate solution. Then, the resulting crude reaction mixture was purified using silica gel column chromatography to obtain the corresponding *γ*-amino alcohol-glycine coupled product (see the respective Table/Scheme for specific entry).

Procedure for the ester hydrolysis of *ortho* C-H arylated *β*-phenylalanine methyl ester carboxamide (Procedure K): To a RB flask containing an appropriate amount of *ortho* C-H arylated *β*-phenylalanine methyl ester carboxamide (1 equiv), THF (2-3 mL) and water (2 M NaOH solution 2-3 mL) were added, and the mixture was stirred at rt for 48 h under ambient air. After the completion of the reaction, the mixture was acidified with 2 N HCl solution and the aqueous layer was extracted with DCM and dried over sodium sulfate. Then the mixture was concentrated in a vacuum and used as such for the next step.

General procedure for the peptide coupling (Procedure L): An appropriate amount of *ortho* C-H arylated beta amino acid (1 equiv), *N*-(3-dimethylaminopropyl)-*N*′-ethylcarbodiimide hydrochloride (1.1 equiv),1-hydroxybenzotriazole hydrate (1.1 equiv), *N,N*diisopropylethylamine (DIPEA) (2 equiv) in DCM (2-4 mL) were stirred at 0 ^oC for 1 h under a nitrogen atm. Then an appropriate amount of L-amino acid methyl ester hydrochloride salt (1 equiv) was added to the above mixture and stirred at rt for 24 h. Then, the resulting solution was subjected to an aq. workup and washed with aq. sodium bicarbonate solution. Then, the resulting crude reaction mixture was purified using silica gel column chromatography

to obtain the corresponding peptide of *ortho* C-H arylated beta amino acid coupled with L-amino acid methyl ester.

Methyl 3-phenyl-3-(picolinamido)propanoate (3a-(RS)): The compound **3a**-(RS) was obtained from procedures A, B and D after purification by column chromatography on silica gel (EtOAc:hexanes = 50:50) as a colourless solid (460 mg, 54%, 3 mmol scale);



R_f (EtOAc/hexanes = 50:50) 0.5;

mp: 112-114 ^oC;

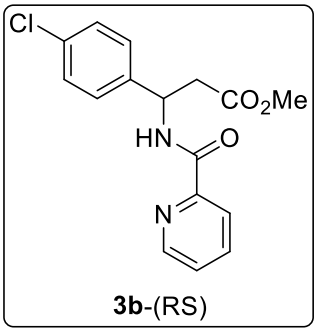
IR (DCM): 3374, 1739, 1519 cm^{-1};

^1H NMR (400 MHz, $CDCl_3$): δ_H 8.90 (1H, d, J = 8.4 Hz), 8.55 (1H, dd, J_1 = 4.7 Hz, J_2 = 0.6 Hz), 8.18 (1H, d, J = 7.8 Hz), 7.82 (1H, td, J_1 = 7.7 Hz, J_2 = 1.7 Hz), 7.43-7.7.40 (3H, m), 7.34 (2H, t, J = 7.7 Hz), 7.28-7.25 (1H, m), 5.67-5.61 (1H, m), 3.63 (3H, s), 3.08 (1H, dd, J_1 = 15.6 Hz, J_2 = 6.5 Hz), 2.96 (1H, dd, J_1 = 15.6 Hz, J_2 = 6.3 Hz);

$^{13}C\{^1H\}$ NMR (~101 MHz, $CDCl_3$): δ_C 171.2, 163.6, 149.6, 148.1, 140.5, 137.2, 128.7, 127.6, 126.3, 126.2, 122.3, 51.8, 49.8, 40.3;

HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{16}H_{17}N_2O_3$: 285.1239; found: 285.1232.

Methyl 3-(4-chlorophenyl)-3-(picolinamido)propanoate (3b-(RS)): The compound **3b**-(RS) was obtained from procedures A, B and D after purification by column chromatography on silica gel (EtOAc:hexanes = 50:50) as a colourless solid (533 mg, 17%, 10 mmol);



R_f (EtOAc/hexanes = 50:50) 0.5;

mp: 119-121 ^oC;

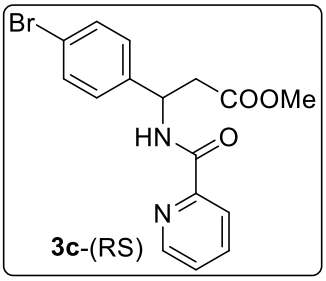
IR (DCM): 3369, 1739, 1676 cm^{-1};

^1H NMR (400 MHz, $CDCl_3$): δ_H 8.96 (1H, d, J = 8.4 Hz), 8.57 (1H, d, J = 4.5 Hz), 8.17 (1H, d, J = 7.8 Hz), 7.83 (1H, t, J = 7.7 Hz), 7.44-7.41 (1H, m), 7.35 (2H, d, J = 8.4 Hz), 7.30 (2H, d, J = 8.6 Hz), 5.63-5.57 (1H, m), 3.64 (3H, s) 3.04 (1H, dd, J_1 = 15.8 Hz, J_2 = 6.3 Hz), 2.95 (1H, dd, J_1 = 15.8 Hz, J_2 = 6.2 Hz);

$^{13}C\{^1H\}$ NMR ($CDCl_3$, ~101.0 MHz): δ_C 171.1, 163.7, 149.5, 148.3, 139.2, 137.4, 133.5, 128.9, 127.9, 126.4, 122.4, 52.0, 49.3, 40.1;

HRMS (ESI): *m/z* $[M + Na]^+$ calcd for $C_{16}H_{15}ClN_2NaO_3$: 341.0669; found: 341.0673.

Methyl 3-(4-bromophenyl)-3-(picolinamido)propanoate (3c-(RS)): The compound **3c**-(RS) was obtained from procedures A, B and D after purification by column chromatography on silica gel (EtOAc:hexanes = 50:50) as a colourless solid (785 mg, 24%, 9 mmol scale);



R_f (EtOAc/hexanes = 50:50) 0.5;

mp: 112-114 ºC;

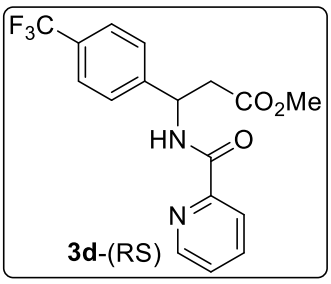
IR (DCM): 3367, 1738, 1516 cm^{-1};

^1H NMR (400 MHz, $CDCl_3$): δ_H 8.95 (1H, d, J = 8.4 Hz), 8.56 (1H, d, J = 4.3 Hz), 8.17 (1H, d, J = 7.8 Hz), 7.83 (1H, t, J = 7.4 Hz), 7.46-7.41 (3H, m), 7.29 (2H, d, J = 8.2 Hz), 5.61-5.55 (1H, m), 3.64 (3H, s), 3.06 (1H, dd, J_1 = 15.8 Hz, J_2 = 6.3 Hz), 2.94 (1H, dd, J_1 = 15.8 Hz, J_2 = 6.2 Hz);

$^{13}C\{^1H\}$ NMR (~101 MHz, $CDCl_3$): δ_C 171.0, 163.6, 149.4, 148.2, 139.7, 137.3, 131.7, 128.1, 126.3, 122.2, 121.5, 51.9, 49.2, 39.9;

HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{16}H_{16}BrN_2O_3$: 363.0344; found: 363.0349.

Methyl 3-(picolinamido)-3-(4-(trifluoromethyl)phenyl)propanoate (3d-(RS)): The compound **3d**-(RS) was obtained from procedures A, B and D after purification by column chromatography on silica gel (EtOAc:hexanes = 50:50) as a colourless solid (917 mg, 26%, 10 mmol);



R_f (EtOAc/hexanes = 50:50) 0.30;

mp: 128-130 ºC;

IR (DCM): 3364, 1674, 1515 cm^{-1};

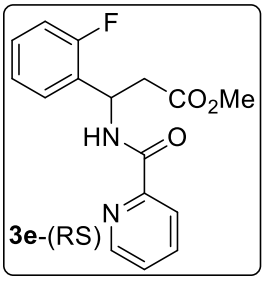
^1H NMR (400 MHz, $CDCl_3$): δ_H 9.03 (1H, d, J = 8.4 Hz), 8.60 (1H, d, J = 4.7 Hz), 8.18 (1H, d, J = 7.8 Hz), 7.86 (1H, td, J_1 = 7.7 Hz, J_2 = 1.6 Hz), 7.60 (2H, d, J = 8.3 Hz), 7.53 (2H, d, J = 8.3 Hz), 7.47-7.44 (1H, m), 5.69-5.64 (1H, m), 3.66 (3H, s), 3.08 (1H, dd, J_1 = 15.9 Hz, J_2 = 6.2 Hz), 2.99 (1H, dd, J_1 = 15.9 Hz, J_2 = 6.0 Hz);

$^{13}C\{^1H\}$ NMR ($CDCl_3$, ~101.0 MHz): δ_C 171.0, 163.9, 149.4, 148.3, 144.7, 137.4, 129.9 (q, JC-F = 33.5 Hz), 126.8, 126.5, 125.7 (q, J_{C-F} = 3.7 Hz), 124.0 (q, J_{C-F} = 272.3 Hz), 122.4, 52.1, 49.5, 40.0;

$^{19}F\{^1H\}$ NMR (~376 MHz, $CDCl_3$): δ_F = -62.57.

HRMS (ESI): *m/z* $[M + H]^+$ calcd for: $C_{17}H_{16}F_3N_2O_3$: 353.1113; found: 353.1103.

Methyl 3-(2-fluorophenyl)-3-(picolinamido)propanoate (3e-(RS)): The compound **3e**-(RS) was obtained from procedures A, B and D after purification by column chromatography on silica gel (EtOAc:hexanes = 50:50) as an orange solid (762 mg, 25%, 10 mmol);



R_f (EtOAc/hexanes = 50:50) 0.3;

mp: 100-102 ^oC;

IR (DCM): 3374, 1738, 1675 cm^{-1};

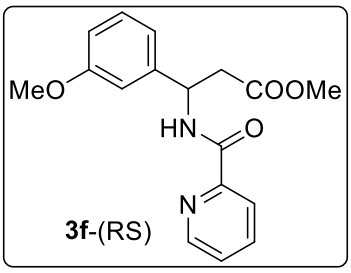
^1H NMR (400 MHz, $CDCl_3$): δ_H 9.04 (1H, d, J = 8.8 Hz), 8.60 (1H, d, J = 4.7 Hz), 8.17 (1H, d, J = 7.8 Hz), 7.83 (1H, td, J_1 = 7.7 Hz, J_2 = 1.3 Hz), 7.45-7.42 (2H, m), 7.28-7.23 (1H, m), 7.12-7.04 (2H, m), 5.86-5.81 (1H, m), 3.63 (3H, s) 3.10 (1H, dd, J_1 = 15.8 Hz, J_2 = 6.5 Hz) 3.00 (1H, dd, J_1 = 15.8 Hz, J_2 = 6.3 Hz);

$^{13}C\{^1H\}$ NMR ($CDCl_3$, ~101.0 MHz): δ_C 171.1, 163.6, 160.6 (d, J_{C-F} = 244.8 Hz), 149.6, 148.3, 137.3, 129.4 (d, J_{C-F} = 8.4 Hz), 128.7 (d, J_{C-F} = 4.3 Hz), 127.5 (d, J_{C-F} = 13.2 Hz), 126.4, 124.3 (d, J_{C-F} = 3.5 Hz), 122.4, 115.8 (d, J_{C-F} = 21.3 Hz), 51.9, 45.8, 39.4;

$^{19}F\{^1H\}$ NMR (~376 MHz, $CDCl_3$): δ_F = -117.69.

HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{16}H_{16}FN_2O_3$: 303.1145; found: 303.1130.

Methyl 3-(3-methoxyphenyl)-3-(picolinamido)propanoate (3f-(RS)): The compound **3f**-(RS) was obtained from procedures A, B and D after purification by column chromatography on silica gel (EtOAc:hexanes = 50:50) as a colourless solid (1.0 g, 58%, 5.5 mmol scale);



R_f (EtOAc/hexanes = 50:50) 0.4;

mp: 98-100 ^oC;

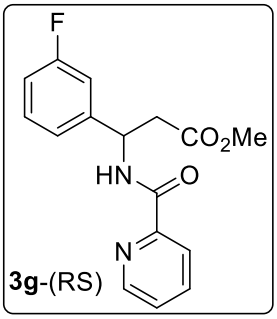
IR (DCM): 3369, 1736, 1514 cm^{-1};

^1H NMR (400 MHz, $CDCl_3$): δ_H 8.88 (1H, d, J = 8.4 Hz), 8.55 (1H, d, J = 4.6 Hz), 8.17 (1H, d, J = 7.8 Hz), 7.82 (1H, t, J = 7.7 Hz), 7.41 (1H, t, J = 6.4 Hz), 7.26 (1H, t, J = 8.5 Hz), 6.99 (1H, d, J = 7.6 Hz), 6.95 (1H, s), 6.80 (1H, d, J = 8.1 Hz), 5.63-5.58 (1H, m), 3.78 (3H, s), 3.64 (3H, s), 3.06 (1H, dd, J_1 = 15.6 Hz, J_2 = 6.6 Hz), 2.95 (1H, dd, J_1 = 15.6 Hz, J_2 = 6.2 Hz);

$^{13}C\{^1H\}$ NMR (~101 MHz, $CDCl_3$): δ_C 171.1, 163.6, 159.7, 149.5, 148.1, 142.2, 137.2, 129.7, 126.2, 122.2, 118.5, 112.8, 112.4, 55.1, 51.8, 49.7, 40.2;

HRMS (ESI): *m/z* $[M + Na]^+$ calcd for $C_{17}H_{18}N_2NaO_4$: 337.1164; found: 337.1174.

Methyl-3-(3-fluorophenyl)-3-(picolinamido)propanoate (3g-(RS)): The compound **3g**-(RS) was obtained from procedures A, B and D after purification by column chromatography on silica gel (EtOAc:hexanes = 50:50) as a brown solid (409 mg, 27%, 5 mmol);



R_f (EtOAc/hexanes = 50:50) 0.35;

mp: 138-140 °C;

IR (DCM): 3375, 1674, 1517 cm^{-1};

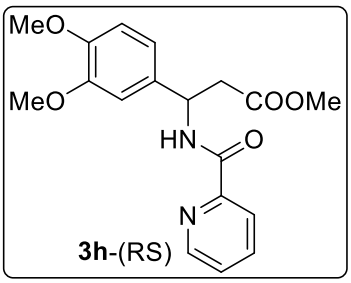
^1H NMR (400 MHz, $CDCl_3$): δ_H 8.96 (1H, d, J = 8.4 Hz), 8.59 (1H, dd, J_1 = 3.8 Hz, J_2 = 0.6 Hz), 8.18 (1H, d, J = 7.8 Hz), 7.85 (1H, td, J_1 = 7.7 Hz, J_2 = 1.6 Hz), 7.46-7.43 (1H, m), 7.34-7.27 (1H, m), 7.18 (1H, d, J = 7.8 Hz) 7.11 (1H, d, J = 9.8 Hz), 6.96 (1H, td, J_1 = 8.4 Hz, J_2 = 1.7 Hz), 5.65-5.60 (1H, m), 3.65 (3H, s), 3.06 (1H, dd, J_1 = 15.8 Hz, J_2 = 6.3 Hz), 2.96 (1H, dd, J_1 = 15.8 Hz, J_2 = 6.0 Hz);

$^{13}C\{^1H\}$ NMR ($CDCl_3$, ~101.0 MHz): δC 171.0, 163.6, 162.9 (d, JC-F = 245.0 Hz), 149.3, 148.1, 143.2 (d, JC-F = 6.7 Hz), 137.3, 130.2 (d, JC-F = 8.2 Hz), 126.3, 122.3, 122.0 (d, JC-F = 2.6 Hz), 114.5 (d, JC-F = 21.0 Hz), 113.4 (d, JC-F = 22.1 Hz), 51.9, 49.3, 40.0;

$^{19}F\{^1H\}$ NMR (~376 MHz, $CDCl_3$): δ_F = -112.37.

HRMS (ESI): *m/z* $[M + H]^+$ calcd for: $C_{16}H_{16}FN_2O_3$: 303.1145; found: 303.1160.

Methyl-3-(3,4-dimethoxyphenyl)-3-(picolinamido)propanoate (3h-(RS)): The compound **3h**-(RS) was obtained from procedures A, B and D after purification by column chromatography on silica gel (EtOAc:hexanes = 50:50) as a brown solid (412 mg, 24%, 5 mmol);



R_f (EtOAc/hexanes = 50:50) 0.25;

mp: 110-127 °C;

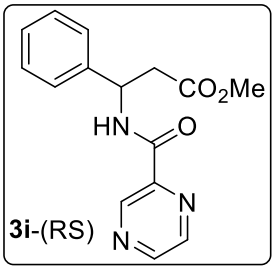
IR (DCM): 3363, 1736, 1671 cm^{-1};

^1H NMR (400 MHz, $CDCl_3$): δ_H 8.81 (1H, d, J = 8.4 Hz), 8.59 (1H, d, J = 4.7 Hz), 8.20 (1H, d, J = 7.8 Hz), 7.85 (1H, td, J_1 = 7.7 Hz, J_2 = 1.6 Hz), 7.46-7.43 (1H, m), 6.99-6.94 (2H, m), 6.85 (1H, d, J = 8.2 Hz), 5.61-5.56 (1H, m), 3.89 (3H, s), 3.87 (3H, s), 3.66 (3H, s), 3.09 (1H, dd, J_1 = 15.5 Hz, J_2 = 6.4 Hz), 2.96 (1H, dd, J_1 = 15.5 Hz, J_2 = 6.5 Hz);

$^{13}C\{^1H\}$ NMR ($CDCl_3$, ~101.0 MHz): δ_C 171.2, 163.5, 149.5, 148.9, 148.4, 148.1, 137.2, 133.2, 126.2, 122.2, 118.3, 111.1, 110.0, 55.8, 55.8, 51.8, 49.6, 40.2;

HRMS (ESI): *m/z* $[M + Na]^+$ calcd for: $C_{18}H_{20}N_2NaO_5$: 367.1270 found: 367.1283.

Methyl 3-phenyl-3-(pyrazine-2-carboxamido)propanoate (3i-(RS)): The compound **3i**-(RS) was obtained procedures A, B and D after purification by column chromatography on silica gel (EtOAc:hexanes = 50:50) as a colourless semi-solid (20 mg, 47%, 0.15 mmol scale);



R_f (EtOAc/hexanes = 50:50) 0.3;

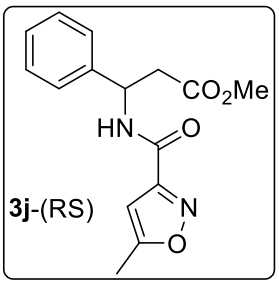
IR (DCM): 3371, 1738, 1522 cm^{-1};

^1H NMR (400 MHz, $CDCl_3$): δ_H 9.40 (1H, s), 8.78-8.75 (2H, m), 8.57 (1H, s), 7.40-7.27 (5H, m), 5.67-5.63 (1H, m), 3.65 (3H, s), 3.08 (1H, dd, J_1 = 15.8 Hz, J_2 = 6.4 Hz), 2.97 (1H, dd, J_1 = 15.8 Hz, J_2 = 6.2 Hz);

$^{13}C\{^1H\}$ NMR ($CDCl_3$, ~101 MHz): δ_C 171.3, 162.4, 147.4, 144.5, 144.3, 142.7, 140.2, 128.9, 127.9, 126.3, 52.0, 49.8, 40.0;

HRMS (ESI): *m/z* $[M + Na]^+$ calcd for $C_{15}H_{15}N_3NaO_3$: 308.1011; found: 308.1002.

Methyl 3-(5-methylisoxazole-3-carboxamido)-3-phenylpropanoate (3j-(RS)): The compound **3j**-(RS) was obtained from procedures A, B and D after purification by column chromatography on silica gel (EtOAc:hexanes = 30:70) as a brown colour semi-solid (23 mg, 53%, 0.15 mmol scale);



R_f (EtOAc/hexanes = 30:70) 0.3;

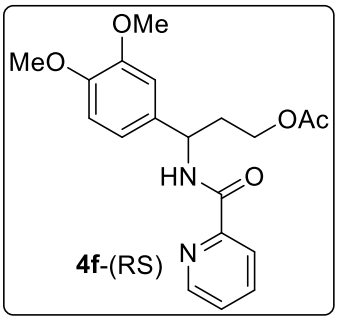
IR (DCM): 3397, 1666, 1465 cm^{-1};

^1H NMR (400 MHz, $CDCl_3$): δ_H 7.71 (1H, d, J = 8.2 Hz), 7.37-7.32 (4H, m), 7.30-7.27 (1H, m), 6.42 (1H, s), 5.61-5.56 (1H, m), 3.63 (3H, s), 3.03 (1H, dd, J_1 = 15.8 Hz, J_2 = 6.4 Hz), 2.93 (1H, dd, J_1 = 15.8 Hz, J_2 = 6.2 Hz), 2.47 (3H, s);

$^{13}C\{^1H\}$ NMR (~101 MHz, $CDCl_3$): δ_C 171.3, 171.1, 158.6, 158.5, 139.9, 128.8, 127.9, 126.4, 101.5, 52.0, 49.8, 39.9, 12.3;

HRMS (ESI): *m/z* $[M + Na]^+$ calcd for $C_{15}H_{16}N_2NaO_4$: 308.1008; found: 308.1004.

3-(3,4-Dimethoxyphenyl)-3-(picolinamido)propyl acetate (4f-(RS)): The compound **4f**-(RS) was obtained from procedures A, C, D and E after purification by column chromatography on silica gel (EtOAc:hexanes = 50:50) as a colourless solid (1.13 g, 79%, 4 mmol scale);



mp: 94-96 ^oC;

R_f (EtOAc/hexanes = 50:50) 0.20;

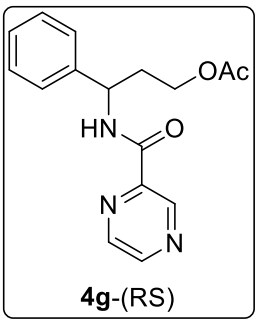
IR (DCM): 3374, 1737, 1516 cm^{-1};

^{1}H NMR (400 MHz, $CDCl_3$): δ_H 8.53-8.49 (2H, m), 8.18 (1H, d, J = 7.5 Hz), 7.83 (1H, t, J = 7.7 Hz), 7.44-7.42 (1H, m), 6.95 (1H, d, J = 8.2 Hz), 6.91 (1H, s), 6.85 (1H, d, J = 8.2 Hz), 5.31-5.25 (1H, m), 4.20-4.10 (2H, m), 3.88 (3H, s), 3.85 (3H, s), 2.34-2.23 (2H, m), 2.07 (3H, s);

^{13}C{^{1}H} NMR (~101 MHz, $CDCl_3$): δ_C 170.8, 163.5, 149.6, 149.0, 148.3, 147.9, 137.3, 133.8, 126.2, 122.2, 118.4, 111.2, 109.9, 61.5, 55.8, 55.8, 50.6, 34.8, 20.8;

HRMS (ESI): *m/z* [M + Na]$^+$ calcd for $C_{19}H_{22}N_2NaO_5$: 381.1426; found: 381.1439.

3-Phenyl-3-(pyrazine-2-carboxamido)propyl acetate (4g-(RS)): The compound **4g**-(RS) was obtained from procedures A, C, D, and E after purification by column chromatography on silica gel (EtOAc:hexanes = 40:60) as a colourless solid (59 mg, 20%, 1 mmol scale);



4g-(RS)

R_f (EtOAc:hexanes = 40:60) 0.3;

mp: 136-138 ^{o}C;

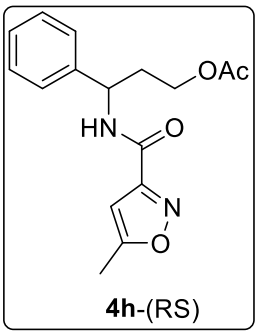
IR (DCM): 3366, 1738, 1520 cm^{-1};

^{1}H NMR (400 MHz, $CDCl_3$): δ_H 9.39 (1H, d, J = 1.4 Hz), 8.75 (1H, d, J = 2.5 Hz), 8.52 (1H, dd, J_1 = 2.4 Hz, J_2 = 1.6 Hz), 8.32 (1H, d, J = 8.4 Hz), 7.39-7.34 (4H, m), 7.31-7.27 (1H, m), 5.36 (1H, dd, J_1 = 15.3 Hz, J_2 = 7.0 Hz), 4.17-4.11 (2H, m), 2.33-2.28 (2H, m), 2.07 (3H, s);

^{13}C{^{1}H} NMR (~101 MHz, $CDCl_3$): δ_C 170.9, 162.3, 147.4, 144.6, 144.3, 142.5, 140.8, 128.9, 127.8, 126.5, 61.4, 51.1, 34.9, 20.9;

HRMS (ESI): *m/z* [M + Na]$^+$ calcd for $C_{16}H_{17}N_3NaO_3$: 322.1168; found: 322.1154.

3-(5-Methylisoxazole-3-carboxamido)-3-phenylpropyl acetate (4h-(RS)): The compound **4h**-(RS) was obtained from procedures A, C, D, and E after purification by column chromatography on silica gel (EtOAc:hexanes = 40:60) as a colourless solid (90 mg, 50%, 0.6 mmol scale);



4h-(RS)

R_f (EtOAc:hexanes = 40:60) 0.3;

mp: 84-86 ^{o}C;

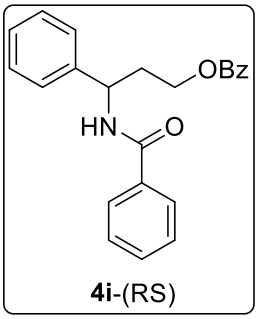
IR (DCM): 3333, 1739, 1542 cm^{-1};

^{1}H NMR (400 MHz, $CDCl_3$): δ_H 7.44 (1H, d, J = 8.1 Hz), 7.35-7.33 (4H, m), 7.29-7.26 (1H, m), 6.42 (1H, s), 5.31 (1H, dd, J_1 = 15.4 Hz, J_2 = 7.1 Hz), 4.16-4.06 (2H, m), 2.45 (3H, s), 2.27-2.22 (2H, m), 2.07 (3H, s);

^{13}C{^{1}H} NMR (~101 MHz, $CDCl_3$): δ_C 171.2, 170.8, 158.5, 158.4, 140.5, 128.8, 127.7, 126.3, 101.4, 61.3, 51.0, 34.6, 20.8, 12.2;

HRMS (ESI): *m/z* $[M + Na]^+$ calcd for $C_{16}H_{18}N_2NaO_4$: 325.1164; found: 325.1166.

3-Benzamido-3-phenylpropyl benzoate acetate (4i-(RS)): The compound **4i**-(RS) was obtained from procedures A, C, D after purification by column chromatography on silica gel (EtOAc:hexanes = 40:60) as a colourless solid (70 mg, 20%, 1 mmol scale);



4i-(RS)

R_f (EtOAc:hexanes = 40:60) 0.5;

mp: 114-116 ^oC;

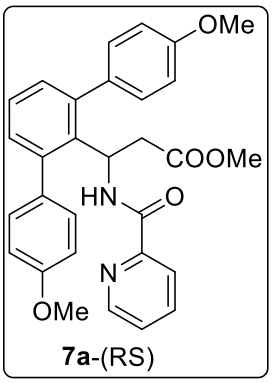
IR (DCM): 3334, 1719, 1523 cm^{-1};

^1H NMR (400 MHz, $CDCl_3$): δ_H 8.00 (2H, d, J = 7.4 Hz), 7.79 (2H, d, J = 7.4 Hz), 7.57 (1H, t, J = 7.4 Hz), 7.50-7.33 (9H, m), 7.30-7.26 (1H, m), 6.98-6.93 (1H, m), 5.45 (1H, dd, J_1 = 14.6 Hz, J_2 = 7.4 Hz), 4.39 (2H, t, J = 6.3 Hz), 2.49-2.35 (2H, m);

$^{13}C\{^1H\}$ NMR (~101 MHz, $CDCl_3$): δ_C 168.8, 166.5, 141.2, 134.2, 133.0, 131.5, 129.9, 129.5, 128.8, 128.4, 128.3, 127.6, 126.9, 126.5, 62.1, 51.6, 34.9;

HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{23}H_{22}NO_3$; 360.1600 found: 360.1601.

Methyl 3-(4,4''-dimethoxy-[1,1':3',1''-terphenyl]-2'-yl)-3-(picolinamido)propanoate (7a-(RS)): The compound **7a**-(RS) was obtained from procedure F after purification by columnchromatography on silica gel (EtOAc:hexanes = 50:50) as a colourless solid (70 mg, 71%, 0.20 mmol scale);



7a-(RS)

R_f (EtOAc/hexanes = 50:50) 0.45;

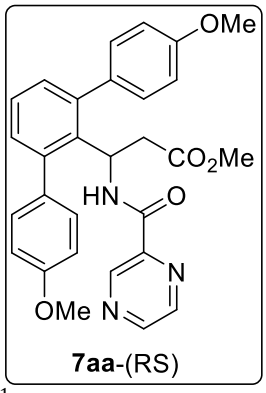
mp: 150-152 ^oC;

IR (DCM): 3373, 1738, 1510 cm^{-1};

^1H NMR (400 MHz, $CDCl_3$): δ_H 8.43 (1H, d, J = 4.4 Hz), 8.06 (1H, d, J = 7.8 Hz), 8.01 (1H, d, J = 8.8 Hz), 7.75 (1H, td, J_1 = 7.7 Hz, J_2 = 1.6 Hz), 7.37-7.24 (6H, m), 7.14 (2H, d, J = 7.5 Hz), 6.94 (4H, br. s), 5.96-5.90 (1H, m), 3.86 (6H, s), 3.43 (3H, s), 2.73 (1H, dd, J_1 = 15.2 Hz, J_2 = 9.7 Hz), 2.63 (1H, dd, J_1 = 15.2 Hz, J_2 = 5.3 Hz);

$^{13}C\{^1H\}$ NMR (~101 MHz, $CDCl_3$): δ_C 170.4, 162.6, 158.7, 149.5, 147.6, 142.0, 136.9, 136.4, 134.0, 130.9, 130.6, 126.4, 125.8, 121.9, 113.5, 55.2, 51.6, 47.8, 41.3;

HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{30}H_{29}N_2O_5$: 497.2076; found: 497.2060.



7aa-(RS)

Methyl 3-(4,4''-dimethoxy-[1,1':3',1''-terphenyl]-2'-yl)-3-(pyrazine-2-carboxamido)propanoate (7aa-(RS)): The compound **7aa**-(RS) was obtained through procedure F after purification by column chromatography on silica gel (EtOAc:hexanes = 50:50) as an orange colour semi-solid (6 mg, <10%, 0.11 mmol);

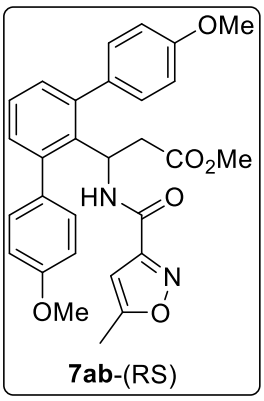
R_f (EtOAc/hexanes = 50:50) 0.4;

IR (DCM): 3729, 1744, 1519 cm^{-1};

^1H NMR (400 MHz, $CDCl_3$): δ_H 9.19 (1H, d, J = 1.4 Hz), 8.61 (1H, d, J = 2.4 Hz), 8.33-8.32 (1H, m), 7.63 (1H, d, J = 10.6 Hz), 7.28-7.19 (6H, m), 7.08 (2H, d, J = 7.5 Hz), 6.88-6.87 (3H, m), 5.89-5.86 (1H, m), 3.80 (6H, s), 3.38 (3H, s), 2.69-2.57 (2H, m); Given the minimum quantity of compound a quality carbon NMR could not be obtained at this stage;

HRMS (ESI): *m/z* $[M + Na]^+$ calcd for $C_{29}H_{27}N_3NaO_5$: 520.1848; found: 520.1839.

Methyl 3-(4,4''-dimethoxy-[1,1':3',1''-terphenyl]-2'-yl)-3-(5-methylisoxazole-3-carboxamido)propanoate (7ab-(RS)): The compound **7ab**-(RS) was obtained through procedure F after purification by column chromatography on silica gel (EtOAc:hexanes = 30:70) as an yellow colour semi-solid (7 mg, <10%, 0.11 mmol);



7ab-(RS)

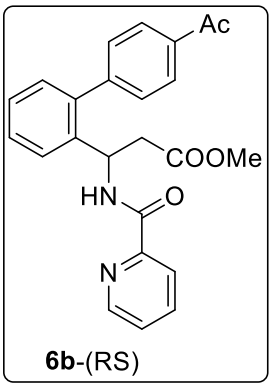
R_f (EtOAc/hexanes = 30:70) 0.4;

IR (DCM): 3400, 1741, 1527 cm^{-1};

^1H NMR (400 MHz, $CDCl_3$): δ_H 7.25-7.19 (5H, m), 7.08 (2H, d, J = 7.4 Hz), 6.91 (4H, d, J = 8.5 Hz), 6.66 (1H, d, J = 8.8 Hz), 6.24-6.23 (1H, m), 5.80-5.78 (1H, m), 3.80 (6H, s), 3.38 (3H, s), 2.56 (1H, dd, J_1 = 16.1 Hz, J_2 = 9.8 Hz), 2.50 (1H, dd, J_1 = 15.4 Hz, J_2 = 5.6 Hz), 2.36 (3H, s); Given the minimum quantity of compound a quality carbon NMR could not be obtained at this stage;

HRMS (ESI): *m/z* $[M + Na]^+$ calcd for $C_{29}H_{28}N_2NaO_6$: 523.1845; found: 523.1855.

Methyl 3-(4'-acetyl-[1,1'-biphenyl]-2-yl)-3-(picolinamido)propanoate (6b-(RS)): The compound **6b**-(RS) was obtained from procedure F after purification by column chromatography on silica gel (EtOAc:hexanes = 50:50) as a colourless solid (8 mg, 19%, 0.10 mmol scale);



6b-(RS)

R_f (EtOAc/hexanes = 50:50) 0.4;

mp: 162-164 ºC;

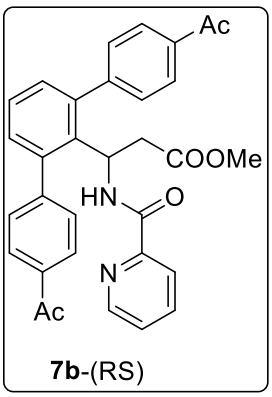
IR (DCM): 3370, 1737, 1514 cm^{-1};

^1H NMR (400 MHz, $CDCl_3$): δ_H 8.99 (1H, d, J = 7.8 Hz), 8.59 (1H, d, J = 4.6 Hz), 8.13 (1H, d, J = 7.8 Hz), 8.06 (2H, d, J = 8.4 Hz), 7.83 (1H, td, J_1 = 7.7 Hz, J_2 = 1.6 Hz), 7.61 (2H, d, J = 8.1 Hz), 7.54 (1H, d, J = 7.5 Hz), 7.45-7.32 (3H, m), 7.22 (1H, dd, J_1 = 7.3 Hz, J_2 = 1.1 Hz), 5.72-5.67 (1H, m), 3.56 (3H, s), 2.78-2.67 (2H, m), 2.66 (3H, s);

$^{13}C\{^1H\}$ NMR (~101 MHz, $CDCl_3$): δ_C 197.9, 171.1, 163.5, 149.6, 148.3, 145.7, 140.3, 138.1, 137.4, 136.0, 130.2, 129.6, 128.6, 128.5, 127.7, 126.3, 125.9, 122.2, 51.9, 47.1, 39.9, 26.7;

HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{24}H_{23}N_2O_4$: 403.1658; found: 403.1641.

Methyl 3-(4,4''-diacetyl-[1,1':3',1''-terphenyl]-2'-yl)-3-(picolinamido)propanoate (7b-(RS)): The compound **7b**-(RS) was obtained from procedure F after purification by column chromatography on silica gel (EtOAc:hexanes = 50:50) as a colourless solid (13 mg, 25%, 0.10 mmol scale);



7b-(RS)

R_f (EtOAc/hexanes = 50:50) 0.3;

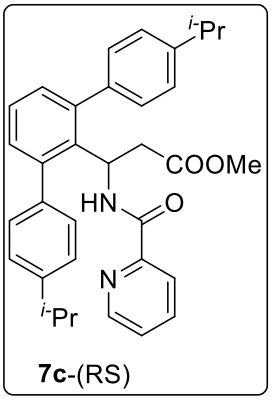
mp: 158-160 ºC;

IR (DCM): 3372, 1739, 1513 cm^{-1};

^1H NMR (400 MHz, $CDCl_3$): δ_H 8.33 (1H, d, J = 4.3 Hz), 8.06-7.33 (13H, m), 7.17 (2H, d, J = 7.6 Hz), 5.83-5.78 (1H, m), 3.43 (3H, s), 2.72 (1H, dd, J_1 = 15.4 Hz, J_2 = 9.9 Hz), 2.66 (6H, s), 2.62 (1H, dd, J_1 = 15.4 Hz, J_2 = 5.1 Hz);

$^{13}C\{^1H\}$ NMR (~101 MHz, $CDCl_3$): δ_C 197.6, 169.9, 162.7, 149.0, 147.7, 146.6, 141.3, 137.1, 135.9, 135.5, 130.7, 129.7, 128.2, 126.7, 126.1, 121.8, 51.7, 47.9, 41.2, 26.6;

HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{32}H_{29}N_2O_5$: 521.2076; found: 521.2055.

Methyl 3-(4,4''-diisopropyl-[1,1':3',1''-terphenyl]-2'-yl)-3-(picolinamido)propanoate (7c-(RS)): 

7c-(RS)

The compound **7c**-(RS) was obtained from procedure F after purification by column chromatography on silica gel (EtOAc:hexanes = 50:50) as a colourless semi-solid (57 mg, 55%, 0.20 mmol scale);

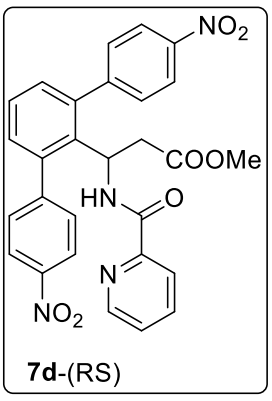
R_f (EtOAc/hexanes = 50:50) 0.6;

IR (DCM): 3370, 1737, 1512 cm^{-1};

^1H NMR (400 MHz, $CDCl_3$): δ_H 8.30 (1H, d, J = 4.6 Hz), 7.98 (1H, d, J = 7.8 Hz), 7.83 (1H, d, J = 8.5 Hz), 7.67 (1H, td, J_1 = 7.7 Hz, J_2 = 1.5 Hz), 7.27-7.16 (10H, m), 7.07 (2H, d, J = 7.6 Hz), 5.85-5.79 (1H, m), 3.32 (3H, s), 2.94-2.84 (2H, m), 2.67 (1H, dd, J_1 = 15.3 Hz, J_2 = 9.7 Hz), 2.57 (1H, dd, J_1 = 15.2 Hz, J_2 = 5.1 Hz), 1.22 (12H, d, J = 7.8 Hz);

$^{13}C\{^1H\}$ NMR (101~MHz, $CDCl_3$): δ_C 170.6, 162.9, 149.7, 147.7, 147.6, 142.4, 139.2, 137.0, 136.2, 130.7, 129.4, 126.4, 126.2, 125.8, 122.0, 51.6, 48.1, 41.7, 33.8, 24.1, 24.0;

HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{34}H_{37}N_2O_3$: 521.2804; found: 521.2806.

Methyl 3-(4,4''-dinitro-[1,1':3',1''-terphenyl]-2'-yl)-3-(picolinamido)propanoate (7d-(RS)): 

7d-(RS)

The compound **7d**-(RS) was obtained from procedure F after purification by column chromatography on silica gel (EtOAc:hexanes = 50:50) as a colourless solid (93 mg, 88%, 0.20 mmol scale);

R_f (EtOAc/hexanes = 50:50) 0.3;

mp: 172-174 ^oC;

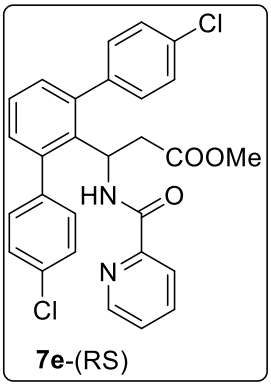
IR (DCM): 3375, 1739, 1516 cm^{-1};

^1H NMR (400 MHz, $CDCl_3$): δ_H 8.35-8.04 (6H, m), 7.85-7.39 (8H, m), 7.21 (2H, d, J = 7.6 Hz), 5.76-5.70 (1H, m), 3.47 (3H, s), 2.70 (1H, dd, J_1 = 15.4 Hz, J_2 = 10.0 Hz), 2.61 (1H, dd, J_1 = 15.4 Hz, J_2 = 5.0 Hz);

$^{13}C\{^1H\}$ NMR (~101 MHz, $CDCl_3$): δ_C 169.5, 162.8, 148.6, 148.2, 147.8, 147.2, 140.2, 137.3, 135.6, 131.0, 130.4, 127.1, 126.5, 123.4, 121.9, 51.9, 47.9, 41.2;

HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{28}H_{23}N_4O_7$: 527.1567; found: 527.1549.

Methyl 3-(4,4''-dichloro-[1,1':3',1''-terphenyl]-2'-yl)-3-(picolinamido)propanoate (7e-(RS)): The compound **7e**-(RS) was obtained from procedure F after purification by column chromatography on silica gel (EtOAc:hexanes = 50:50) as a colourless solid (85 mg, 84%, 0.20 mmol scale);



7e-(RS)

R_f (EtOAc/hexanes = 50:50) 0.6;

mp: 104-106 ^oC;

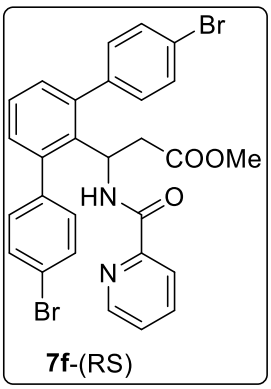
IR (DCM): 3375, 1738, 1511 cm^{-1};

^1H NMR (400 MHz, $CDCl_3$): δ_H 8.44 (1H, d, J = 4.5 Hz), 8.04 (1H, d, J = 7.8 Hz), 7.85 (1H, d, J = 8.5 Hz), 7.77 (1H, t, J = 7.7 Hz), 7.40-7.26 (10H, m), 7.13 (2H, d, J = 7.6 Hz), 5.86-5.81 (1H, m), 3.45 (3H, s), 2.71 (1H, dd, J_1 = 15.3 Hz, J_2 = 10.0 Hz), 2.61 (1H, dd, J_1 = 15.3 Hz, J_2 = 5.0 Hz);

$^{13}C\{^1H\}$ NMR (~101 MHz, $CDCl_3$): δ_C 170.0, 162.7, 149.0, 147.8, 141.0, 140.0, 137.0, 136.0, 133.3, 130.9, 130.7, 128.3, 126.6, 126.0, 121.7, 51.7, 47.7, 41.4;

HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{28}H_{23}Cl_2N_2O_3$: 505.1086; found: 505.1096.

Methyl 3-(4,4''-dibromo-[1,1':3',1''-terphenyl]-2'-yl)-3-(picolinamido)propanoate (7f-(RS)): The compound **7f**-(RS) was obtained from procedure F after purification by column chromatography on silica gel (EtOAc:hexanes = 50:50) as a colourless solid (85 mg, 57%, 0.25 mmol scale);



7f-(RS)

R_f (EtOAc/hexanes = 50:50) 0.6;

mp: 112-114 ^oC;

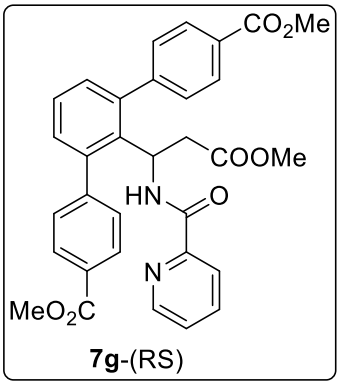
IR (DCM): 3374, 1739, 1459 cm^{-1};

^1H NMR (400 MHz, $CDCl_3$): δ_H 8.38 (1H, d, J = 4.6 Hz), 7.94 (1H, d, J = 7.8 Hz), 7.75 (1H, d, J = 8.4 Hz), 7.68 (1H, td, J_1 = 7.7 Hz, J_2 = 1.5 Hz), 7.43-7.18 (10H, m), 7.04 (2H, d, J = 7.6 Hz), 5.78-5.72 (1H, m), 3.36 (3H, s), 2.62 (1H, dd, J_1 = 15.3 Hz, J_2 = 10.0 Hz), 2.51 (1H, dd, J_1 = 15.2 Hz, J_2 = 5.0 Hz);

$^{13}C\{^1H\}$ NMR (~101 MHz, $CDCl_3$): δ_C 170.0, 162.7, 149.0, 147.8, 141.0, 140.5, 137.1, 135.9, 131.3, 131.0, 130.8, 126.7, 126.1, 121.8, 121.5, 51.7, 47.8, 41.5;

HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{28}H_{23}Br_2N_2O_3$: 593.0075; found: 593.0079.

Dimethyl 2'-(3-methoxy-3-oxo-1-(picolinamido)propyl)-[1,1':3',1''-terphenyl]-4,4''-dicarboxylate (7g-(RS)): The compound **7g**-(RS) was obtained from procedure F after purification by column chromatography on silica gel (EtOAc:hexanes = 50:50) as a colourless solid (90 mg, 65%, 0.25 mmol scale);



7g-(RS)

R_f (EtOAc/hexanes = 50:50) 0.3;

mp: 139-141 ^oC;

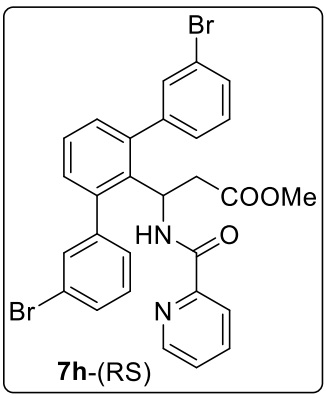
IR (DCM): 3374, 1722, 1512 cm^{-1};

^1H NMR (400 MHz, $CDCl_3$): δ_H 8.28 (1H, d, J = 4.4 Hz), 8.01-7.95 (5H, m), 7.74-7.68 (2H, m), 7.42-7.24 (6H, m), 7.10 (2H, d, J = 7.6 Hz), 5.75-5.69 (1H, m), 3.89 (6H, s), 3.35 (3H, s), 2.61 (1H, dd, J_1 = 15.3 Hz, J_2 = 9.8 Hz), 2.52 (1H, dd, J_1 = 15.3 Hz, J_2 = 5.1 Hz);

$^{13}C\{^1H\}$ NMR (~101 MHz, $CDCl_3$): δ_C 170.0, 166.9, 162.8, 149.1, 147.8, 146.5, 141.5, 137.1, 135.7, 130.7, 129.6, 129.6, 129.2, 126.8, 126.1, 121.9, 52.2, 51.8, 47.9, 41.3;

HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{32}H_{29}N_2O_7$: 553.1975; found: 553.1976.

Methyl 3-(3,3''-dibromo-[1,1':3',1''-terphenyl]-2'-yl)-3-(picolinamido)propanoate (7h-(RS)): The compound **7h**-(RS) was obtained from procedure F after purification by column chromatography on silica gel (EtOAc:hexanes = 50:50) as a colourless semi-solid (62 mg, 52%, 0.20 mmol scale);



7h-(RS)

R_f (EtOAc/hexanes = 50:50) 0.6;

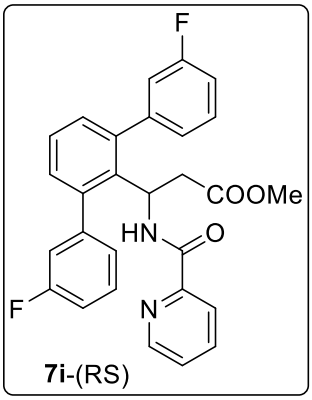
IR (DCM): 3374, 1740, 1512 cm^{-1};

^1H NMR (400 MHz, $CDCl_3$): δ_H 8.50 (1H, d, J = 3.4 Hz), 8.06 (1H, d, J = 7.8 Hz), 7.94 (1H, d, J = 8.2 Hz), 7.76 (1H, td, J_1 = 7.7 Hz, J_2 = 1.5 Hz), 7.53-7.26 (10H, m), 7.15 (2H, d, J = 7.6 Hz), 5.82-5.77 (1H, m), 3.48 (3H, s), 2.74-2.64 (2H, m);

$^{13}C\{^1H\}$ NMR (~101 MHz, $CDCl_3$): δ_C 170.0, 162.8, 149.1, 148.2, 143.5, 140.8, 137.0, 135.8, 132.4, 130.9, 130.4, 129.6, 128.2, 126.7, 126.0, 122.3, 121.9, 51.8, 47.7, 41.4;

HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{28}H_{23}Br_2N_2O_3$: 593.0075; found: 593.0079.

Methyl 3-(3,3''-difluoro-[1,1':3',1''-terphenyl]-2'-yl)-3-(picolinamido)propanoate (7i-(RS)): The compound **7i**-(RS) was obtained from procedure F after purification by column chromatography on silica gel (EtOAc:hexanes = 50:50) as a colourless solid (76 mg, 80%, 0.20 mmol scale);



7i-(RS)

R_f (EtOAc/hexanes = 50:50) 0.65;

mp: 148-150 ^{o}C;

IR (DCM): 3372, 1738, 1510 cm^{-1};

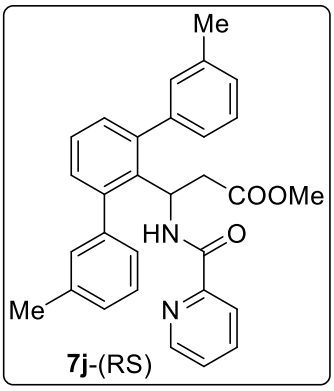
1H NMR (400 MHz, $CDCl_3$): δ_H 8.43 (1H, d, J = 4.4 Hz), 8.05 (1H, d, J = 7.8 Hz), 7.95 (1H, d, J = 8.4 Hz), 7.76 (1H, t, J = 7.6 Hz), 7.38-7.07 (12H, m), 5.88-5.82 (1H, m), 3.46 (3H, s), 2.72 (1H, dd, J_1 = 15.2 Hz, J_2 = 9.8 Hz), 2.63 (1H, dd, J_1 = 15.2 Hz, J_2 = 5.1 Hz);

$^{13}C\{^1H\}$ NMR (~101 MHz, $CDCl_3$): δ_C 170.1, 162.7, 162.4 (d, J_{C-F} = 245.6 Hz), 149.2, 147.8, 143.5 (d, J_{C-F} = 7.5 Hz), 141.0, 137.0, 135.9, 130.7, 129.6 (d, J_{C-F} = 8.3 Hz), 126.6, 126.0, 125.3 (d, J_{C-F} = 2.6 Hz), 121.9, 116.8 (d, J_{C-F} = 21.4 Hz), 114.3 (d, J_{C-F} = 20.7 Hz), 51.7, 47.7, 41.4;

$^{19}F\{^1H\}$ NMR (~376 MHz, $CDCl_3$): δ_F = -112.56, -113.11.

HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{28}H_{23}F_2N_2O_3$: 473.1677; found: 473.1672.

Methyl 3-(3,3''-dimethyl-[1,1':3',1''-terphenyl]-2'-yl)-3-(picolinamido)propanoate (7j-(RS)): The compound **7j**-(RS) was obtained from procedure F after purification by column chromatography on silica gel (EtOAc:hexanes = 50:50) as a colourless semi-solid (62 mg, 53%, 0.25 mmol scale);



7j-(RS)

R_f (EtOAc/hexanes = 50:50) 0.6;

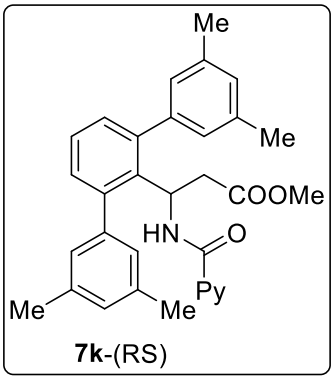
IR (DCM): 3375, 1739, 1511 cm^{-1};

^1H NMR (400 MHz, $CDCl_3$): δ_H 8.35 (1H, d, J = 4.5 Hz), 7.99 (1H, d, J = 7.8 Hz), 7.93 (1H, br. s), 7.67 (1H, td, J_1 = 7.7 Hz, J_2 = 1.6 Hz), 7.28-7.17 (6H, m), 7.11-7.07 (6H, m), 5.82-5.76 (1H, m), 3.35 (3H, s), 2.62 (1H, dd, J_1 = 15.2 Hz, J_2 = 9.4 Hz), 2.53 (1H, dd, J_1 = 15.2 Hz, J_2 = 5.5 Hz), 2.24 (6H, br. s);

$^{13}C\{^1H\}$ NMR (~76 MHz, $CDCl_3$): δ_C 170.5, 162.6, 149.7, 147.8, 142.6, 141.7, 137.7, 136.9, 135.7, 130.5, 130.3, 128.0, 128.0, 126.6, 126.4, 125.8, 122.1, 51.5, 47.9, 41.3, 21.4;

HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{30}H_{29}N_2O_3$: 465.2178; found: 465.2184.

Methyl 3-(picolinamido)-3-(3,3'',5,5''-tetramethyl-[1,1':3',1''-terphenyl]-2'-yl)propanoate (7k-(RS)): The compound **7k**-(RS) was obtained from procedure F after purification by column chromatography on silica gel (EtOAc:hexanes = 50:50) as a colourless solid (59 mg, 60%, 0.20 mmol scale);



7k-(RS)

R_f (EtOAc/hexanes = 50:50) 0.6;

mp: 163-165 ^oC;

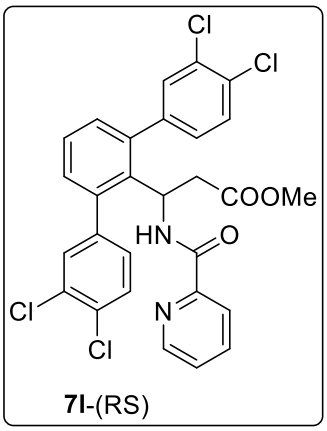
IR (DCM): 3372, 1738, 1510 cm^{-1};

^1H NMR (400 MHz, $CDCl_3$): δ_H 8.38 (1H, d, J = 4.7 Hz), 8.04 (1H, d, J = 8.7 Hz), 8.00 (1H, d, J = 7.8 Hz), 7.68 (1H, td, J_1 = 7.7 Hz, J_2 = 1.5 Hz), 7.30-7.26 (1H, m), 7.20-7.16 (1H, m), 7.07 (2H, d, J = 7.5 Hz), 6.93 (6H, br. s), 5.81-5.75 (1H, m), 3.37 (3H, s), 2.60 (1H, dd, J_1 = 15.2 Hz, J_2 = 8.9 Hz), 2.53 (1H, dd, J_1 = 15.2 Hz, J_2 = 6.1 Hz), 2.25 (12H, br. s);

$^{13}C\{^1H\}$ NMR (~101 MHz, $CDCl_3$): δ_C 170.7, 162.5, 149.9, 147.9, 142.8, 141.7, 137.6, 137.0, 135.6, 130.4, 128.9, 127.5, 126.4, 125.8, 122.1, 51.5, 47.9, 41.3, 21.4;

HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{32}H_{33}N_2O_3$: 493.2491; found: 493.2487.

Methyl 3-(picolinamido)-3-(3,3'',4,4''-tetrachloro-[1,1':3',1''-terphenyl]-2'-yl)propanoate (7l-(RS)): The compound **7l**-(RS) was obtained from procedure F after purification by column chromatography on silica gel (EtOAc:hexanes = 50:50) as a colourless solid (75 mg, 65%, 0.20 mmol scale);



7l-(RS)

R_f (EtOAc/hexanes = 50:50) 0.7;

mp: 121-123 ^oC;

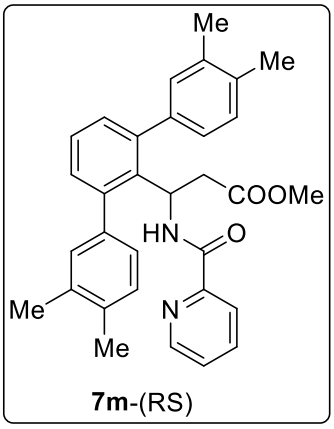
IR (DCM): 3375, 1739, 1510 cm^{-1};

^1H NMR (400 MHz, $CDCl_3$): δ_H 8.50 (1H, d, J = 4.5 Hz), 8.07 (1H, d, J = 7.8 Hz), 7.90 (1H, d, J = 8.2 Hz), 7.80 (1H, td, J_1 = 7.7 Hz, J_2 = 1.2 Hz), 7.53-7.31 (8H, m), 7.16 (2H, d, J = 7.6 Hz), 5.82-5.77 (1H, m), 3.51 (3H, s), 2.72 (1H, dd, J_1 = 15.2 Hz, J_2 = 9.6 Hz), 2.64 (1H, dd, J_1 = 15.2 Hz, J_2 = 5.3 Hz);

$^{13}C\{^1H\}$ NMR (~101 MHz, $CDCl_3$): δ_C 169.9, 162.9, 148.9, 148.3, 141.4, 140.0, 137.2, 136.1, 132.5, 131.8, 131.5, 131.2, 130.2, 128.9, 127.0, 126.2, 121.9, 52.0, 47.9, 41.6;

HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{28}H_{21}Cl_4N_2O_3$: 573.0306; found: 573.0297.

Methyl 3-(picolinamido)-3-(3,3'',4,4''-tetramethyl-[1,1':3',1''-terphenyl]-2'-yl)propanoate (7m-(RS)): The compound **7m**-(RS) was obtained from procedure F after purification by column chromatography on silica gel (EtOAc:hexanes = 50:50) as a colourless semi-solid (66 mg, 54%, 0.25 mmol scale);



7m-(RS)

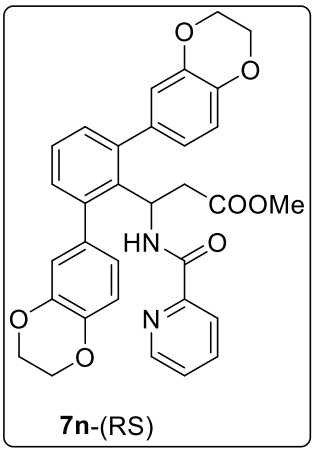
R_f (EtOAc/hexanes = 50:50) 0.7;

IR (DCM): 3377, 1738, 1505 cm^{-1};

^1H NMR (400 MHz, $CDCl_3$): δ_H 8.43 (1H, dt, J_1 = 1.4 Hz, J_2 = 0.6 Hz), 8.08-8.06 (2H, m), 7.75 (1H, td, J_1 = 7.7 Hz, J_2 = 1.7 Hz), 7.37-7.33 (1H, m), 7.28-7.13 (9H, m), 5.93-5.87 (1H, m), 3.43 (3H, s), 2.71 (1H, dd, J_1 = 15.2 Hz, J_2 = 9.2 Hz), 2.63 (1H, dd, J_1 = 15.3 Hz, J_2 = 5.8 Hz), 2.31 (6H, s), 2.23 (6H, br. s);

$^{13}C\{^1H\}$ NMR (~101 MHz, $CDCl_3$): δ_C 170.6, 162.5, 149.8, 147.7, 142.5, 139.4, 136.9, 136.2, 135.8, 135.4, 130.8, 130.5, 129.3, 126.9, 126.4, 125.7, 122.0, 51.5, 47.9, 41.2, 19.7, 19.5;

HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{32}H_{33}N_2O_3$: 493.2491; found: 493.2498.



7n-(RS)

Methyl 3-(2,6-bis(2,3-dihydrobenzo[*b*][1,4]dioxin-6-yl)phenyl)-3-(picolinamido)propanoate (7n-(RS)): The compound **7n**-(RS) was obtained from procedure F after purification by column chromatography on silica gel (EtOAc:hexanes = 50:50) as a brown solid (87 mg, 63%, 0.25 mmol scale);

R_f (EtOAc/hexanes = 50:50) 0.3;

mp: 183-185 ^oC

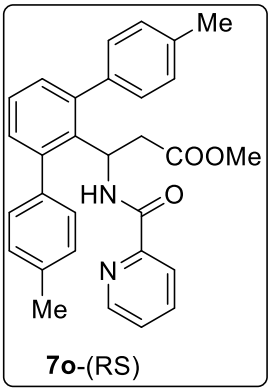
IR (DCM): 3368, 1738, 1507 cm^{-1};

^1H NMR (400 MHz, $CDCl_3$): δ_H 8.48-8.46 (1H, m), 8.13 (1H, d, J = 8.8 Hz), 8.06 (1H, dt, J_1 = 7.8 Hz, J_2 = 1.0 Hz), 7.76 (1H, td, J_1 = 7.7 Hz, J_2 = 1.7 Hz), 7.37-7.34 (1H, m), 7.26-7.22 (1H, m), 7.13 (2H, d, J = 7.2 Hz), 6.89 (6H, br. s), 5.97-5.91 (1H, m), 4.31-4.23 (8H, m), 3.48 (3H, s), 2.78 (1H, dd, J_1 = 15.2 Hz, J_2 = 9.6 Hz), 2.68 (1H, dd, J_1 = 15.2 Hz, J_2 = 5.4 Hz);

$^{13}C\{^1H\}$ NMR (~126 MHz, $CDCl_3$): δ_C 170.6, 162.7, 149.8, 147.8, 143.1, 142.9, 141.8, 137.0, 136.3, 135.1, 130.9, 126.4, 125.8, 122.8, 122.0, 118.6, 116.9, 64.4, 51.6, 47.9, 41.6;

HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{32}H_{29}N_2O_7$: 553.1975; found: 553.1991.

Methyl 3-(4,4''-dimethyl-[1,1':3',1''-terphenyl]-2'-yl)-3-(picolinamido)propanoate (7o-(RS)): The compound **7o**-(RS) was obtained from procedure F after purification by column chromatography on silica gel (EtOAc:hexanes = 50:50) as a colourless solid (60 mg, 65%, 0.20 mmol scale);



7o-(RS)

R_f (EtOAc/hexanes = 50:50);

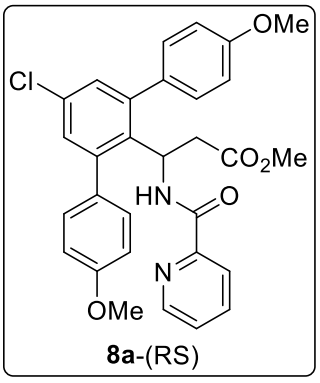
mp: 137-139 ºC;

IR (DCM): 3373, 1739, 1512 cm^{-1};

^1H NMR (400 MHz, $CDCl_3$): δ_H 8.44-8.42 (1H, m), 8.05 (1H, dt, J_1 = 7.8 Hz, J_2 = 1.1 Hz), 8.00 (1H, d, J = 8.7 Hz), 7.76 (1H, td, J_1 = 7.7 Hz, J_2 = 1.7 Hz), 7.38-7.22 (10H, m), 7.15 (2H, d, J = 7.4 Hz), 5.92-5.86 (1H, m), 3.42 (3H, s), 2.71 (1H, dd, J_1 = 15.3 Hz, J_2 = 9.6 Hz), 2.61 (1H, dd, J_1 = 15.3 Hz, J_2 = 5.5 Hz), 2.42 (6H, s);

$^{13}C\{^1H\}$ NMR (~101 MHz, $CDCl_3$): δ_C 170.6, 162.6, 149.6, 147.5, 142.4, 138.9, 137.2, 136.8, 136.1, 130.8, 129.4, 128.9, 126.5, 125.9, 122.1, 51.6, 47.9, 41.3, 21.3;

HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{30}H_{29}N_2O_3$: 465.2178; found: 465.2162.



8a-(RS)

Methyl 3-(5'-chloro-4,4''-dimethoxy-[1,1':3',1''-terphenyl]-2'-yl)-3-(picolinamido)propanoate (8a-(RS)): The compound **8a**-(RS) was obtained through procedure F after purification by column chromatography on silica gel (EtOAc:hexanes = 50:50) as a colourless solid (50 mg, 63%, 0.15 mmol);

R_f (EtOAc/hexanes = 50:50) 0.4;

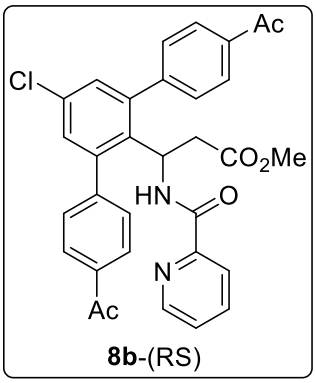
mp: 140-142 ºC;

IR (DCM): 3375, 1677, 1506 cm^{-1};

^1H NMR (400 MHz, $CDCl_3$): δ_H 8.43 (1H, d, J = 4.7 Hz), 8.06 (1H, d, J = 7.8 Hz), 7.96 (1H, d, J = 8.6 Hz), 7.77 (1H, td, J_1 = 7.7 Hz, J_2 = 1.7 Hz), 7.39-7.26 (5H, m), 7.15 (2H, s), 6.94 (4H, br. s), 5.88-5.82 (1H, m), 3.86 (6H, s), 3.44 (3H, s), 2.70 (1H, dd, J_1 = 15.3 Hz, J_2 = 9.6 Hz), 2.57 (1H, dd, J_1 = 15.3 Hz, J_2 = 5.5 Hz);

$^{13}C\{^1H\}$ NMR ($CDCl_3$, ~76.0 MHz): δ_C 170.3, 162.8, 159.1, 149.5, 147.7, 143.9, 137.1, 135.3, 132.8, 131.9, 130.6, 130.5, 126.0, 122.0, 113.7, 55.3, 51.7, 47.5, 41.1;

HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{30}H_{28}ClN_2O_5$: 531.1687; found: 531.1702.



Methyl 3-(4,4''-diacetyl-5'-chloro-[1,1':3',1''-terphenyl]-2'-yl)-3-(picolinamido)propanoate (8b-(RS)): The compound **8b**-(RS) was obtained through procedure F after purification by column chromatography on silica gel (EtOAc:hexanes = 50:50) as a yellow solid (67 mg, 81%, 0.15 mmol);

R_f (EtOAc/hexanes = 50:50) 0.30;

mp: 190-192 ^oC;

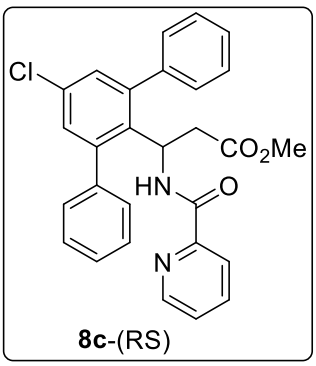
IR (DCM): 3374, 1679, 1510 cm^{-1};

^1H NMR (400 MHz, CDCl3): δ_H 8.34 (1H, d, J = 4.7 Hz), 8.05-7.38 (12H, m), 7.18 (2H, s), 5.73-5.70 (1H, m), 3.44 (3H, s), 2.66 (6H, s), 2.68 (1H, dd, J_1 = 15.5 Hz, J_2 = 10.0 Hz), 2.58 (1H, dd, J_1 = 15.4 Hz, J_2 = 5.1 Hz);

$^{13}C\{^1H\}$ NMR ($CDCl_3$, ~101 MHz): δ_C 197.6, 169.8, 162.9, 148.9, 147.8, 145.2, 143.0, 137.3,136.4, 134.5, 132.4, 130.5, 129.7, 128.4, 126.3, 122.0, 51.9, 47.6, 41.1, 26.8;

HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{32}H_{28}ClN_2O_5$: 555.1687; found: 555.1698.

Methyl 3-(5'-chloro-[1,1':3',1''-terphenyl]-2'-yl)-3-(picolinamido)propanoate (8c-(RS)):



The compound **8c**-(RS) was obtained through procedure F after purification by column chromatography on silica gel (EtOAc:hexanes = 50:50) as a brown solid (67 mg, 95%, 0.15 mmol);

R_f (EtOAc/hexanes = 50:50) 0.60;

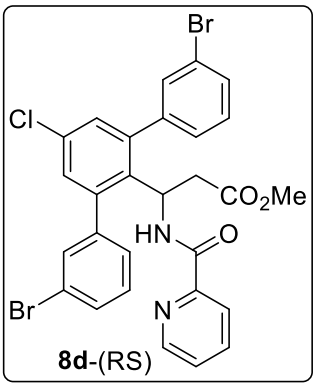
mp: 110-112 ^oC,

IR (DCM): 3377, 1680, 1510 cm^{-1};

^1H NMR (400 MHz, $CDCl_3$): δ_H 8.41 (1H, d, J = 4.2 Hz), 8.05 (1H, d, J = 7.7 Hz), 7.89 (1H, d, J = 8.2 Hz), 7.77 (1H, t, J = 7.4 Hz), 7.55-7.26 (11H, m), 7.18 (2H, s), 5.83-5.77 (1H, m), 3.43 (3H, s), 2.69 (1H, dd, J_1 = 15.4 Hz, J_2 = 9.7 Hz), 2.57 (1H, dd, J_1 = 15.4 Hz, J_2 = 5.2 Hz);

$^{13}C\{^1H\}$ NMR ($CDCl_3$, ~101 MHz): δ_C 170.2, 162.7, 149.3, 147.7, 144.1, 140.4, 137.1, 134.7, 132.0, 130.4, 129.3, 128.3, 127.7, 126.0, 122.0, 51.7, 47.5, 41.1;

HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{28}H_{24}ClN_2O_3$: 471.1475 found: 471.1485.



Methyl 3-(3,3''-dibromo-5'-chloro-[1,1':3',1''-terphenyl]-2'-yl)-3-(picolinamido)propanoate (8d-(RS)): The compound **8d**-(RS) was obtained through procedure F after purification by column chromatography on silica gel (EtOAc:hexanes = 50:50) as a green solid (74 mg, 78%, 0.15 mmol);

R_f (EtOAc/hexanes = 50:50) 0.65;

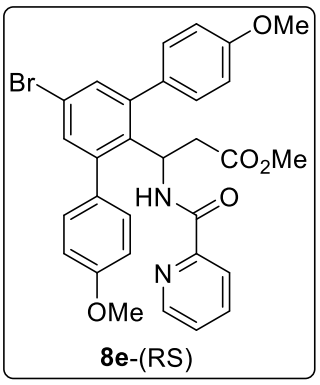
mp: 90-92 ^oC;

IR (DCM): 3375, 1677, 1506 cm^{-1};

^1H NMR (400 MHz, CDCl3): δ_H 8.50 (1H, d, J = 3.1 Hz), 8.06 (1H, d, J = 7.8 Hz), 7.89 (1H, d, J = 8.0 Hz), 7.79 (1H, td, J_1 = 7.7 Hz, J_2 = 1.7 Hz), 7.56-7.37 (7H, m), 7.26 (2H, s), 7.17 (2H, s), 5.72-5.70 (1H, m), 3.50 (3H, s), 2.68 (1H, dd, J_1 = 15.2 Hz, J_2 = 9.4 Hz) 2.62-2.60 (1H, m);

$^{13}C\{^1H\}$ NMR ($CDCl_3$, ~101 MHz): δ_C 170.0, 162.9, 149.0, 148.4, 142.6, 142.2, 137.2, 134.8, 132.3, 131.0, 130.7, 129.9, 128.1, 126.2, 122.6, 122.0, 52.0, 47.5, 40.8;

HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{28}H_{22}Br_2ClN_2O_3$:626.9686; found: 626.9713.



Methyl 3-(5'-bromo-4,4''-dimethoxy-[1,1':3',1''-terphenyl]-2'-yl)-3-(picolinamido)propanoate (8e-(RS)): The Compound **8e**-(RS) was obtained through procedure F after purification by column chromatography on silica gel (EtOAc:hexanes = 50:50) as a yellow solid (80 mg, 93%, 0.15 mmol);

R_f (EtOAc/hexanes = 50:50) 0.40;

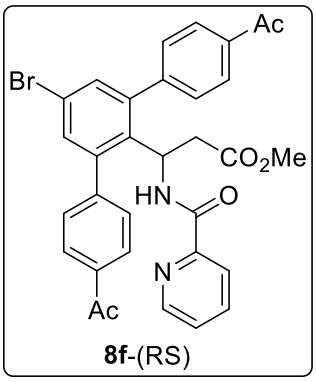
mp: 198-200 ^oC;

IR (DCM): 3375, 1677, 1507 cm^{-1};

^1H NMR (400 MHz, $CDCl_3$): δ_H 8.44-8.42 (1H, m), 8.05 (1H, dt, J_1 = 1.8 Hz, J_2 = 0.9 Hz) 7.96 (1H, d, J = 8.6 Hz), 7.77 (1H, td, J_1 = 7.7 Hz, J_2 = 1.7 Hz), 7.39-7.26 (7H, m), 6.95 (4H, br. s), 5.87-5.81 (1H, m), 3.86 (6H, s), 3.45 (3H, s), 2.70 (1H, dd, J_1 = 15.4 Hz, J_2 = 9.7 Hz), 2.59 (1H, dd, J_1 = 15.3 Hz, J_2 = 5.4 Hz);

$^{13}C\{^1H\}$ NMR ($CDCl_3$, ~101 MHz): δ_C 170.3, 162.8, 159.1, 149.4, 147.7, 144.1, 137.1, 135.8, 133.5, 132.7, 130.5, 126.0, 122.0, 120.2, 113.7, 55.3, 51.7, 47.6, 41.1;

HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{30}H_{28}BrN_2O_5$: 575.1182 found: 575.1207.



Methyl 3-(4,4''-diacetyl-5'-bromo-[1,1':3',1''-terphenyl]-2'-yl)-3-(picolinamido)propanoate (8f-(RS)): The compound **8f**-(RS) was obtained through procedure F after purification by column chromatography on silica gel (EtOAc:hexanes = 50:50) as a yellow solid (70 mg, 78%, 0.15 mmol);

R_f (EtOAc/hexanes = 50:50) 0.30;

mp: 190-192 ^oC;

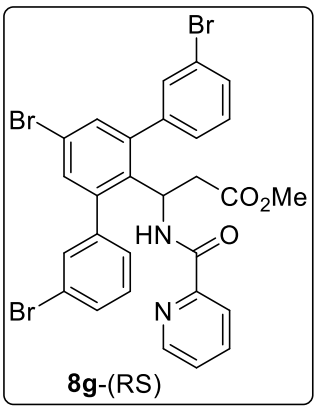
IR (DCM): 3372, 1680, 1511 cm^{-1};

^1H NMR (400 MHz, $CDCl_3$): δ_H 8.33 (1H, d, J = 4.7 Hz), 8.05-8.00 (4H, m), 7.82-7.38 (8H, m), 7.34 (2H, s), 5.71-5.69 (1H, m), 3.44 (3H, s), 2.72-2.68 (1H, m), 2.66 (6H, s), 2.58 (1H, dd, J_1 = 15.4 Hz, J_2 = 5.2 Hz);

$^{13}C\{^1H\}$ NMR ($CDCl_3$, ~101 MHz): δ_C 197.7, 169.8, 162.9, 148.9, 147.8, 145.1, 143.2, 137.3, 136.4, 135.0, 133.3, 129.7, 128.4, 126.3, 122.0, 120.6, 51.9, 47.6, 41.0, 26.8;

HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{32}H_{28}BrN_2O_5$; 599.1182 found: 599.1196.

Methyl 3-(picolinamido)-3-(3,3'',5'-tribromo-[1,1':3',1''-terphenyl]-2'-yl)propanoate (8g-(RS)): The compound **8g**-(RS) was obtained through procedure F after purification by column chromatography on silica gel (EtOAc:hexanes = 50:50) as a yellow solid (66 mg, 65%, 0.15 mmol);



R_f (EtOAc/hexanes = 50:50) 0.60;

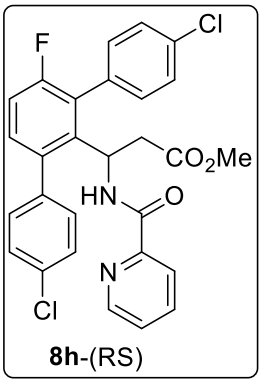
mp: 151-153 ^oC;

IR (DCM): 3375, 1740, 1678 cm^{-1};

^1H NMR (400 MHz, $CDCl_3$): δ_H 8.50 (1H, d, J = 3.3 Hz), 8.06 (1H, d, J = 7.8 Hz), 7.89 (1H, d, J = 8.0 Hz), 7.77 (1H, td, J_1 = 7.7 Hz, J_2 = 1.7 Hz), 7.55-7.32 (11H, m), 5.74-5.68 (1H, m), 3.50 (3H, s), 2.68 (1H, dd, J_1 = 15.2 Hz, J_2 = 9.5 Hz), 2.59 (1H, dd, J_1 = 10.8 Hz, J_2 = 0.2 Hz);

$^{13}C\{^1H\}$ NMR ($CDCl_3$, ~101 MHz): δ_C 169.8, 162.8, 148.9, 148.2, 142.6, 142.0, 137.1, 135.2, 133.5, 132.3, 130.9, 129.8, 128.0, 126.1, 122.5, 121.9, 120.4, 51.9, 47.4, 41.1;

HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{28}H_{22}Br_3N_2O_3$: 670.9181 found: 670.9180.



Methyl 3-(4,4''-dichloro-4'-fluoro-[1,1':3',1''-terphenyl]-2'-yl)-3-(picolinamido)propanoate (8h-(RS)): The compound **8h**-(RS) was obtained through procedure F after purification by column chromatography on silica gel (EtOAc:hexanes = 50:50) as a yellow colour semi-solid (101 mg, 77%, 0.25 mmol);

R_f (EtOAc/hexanes = 50:50) 0.55;

IR (DCM): 3375, 1740, 1678 cm^{-1};

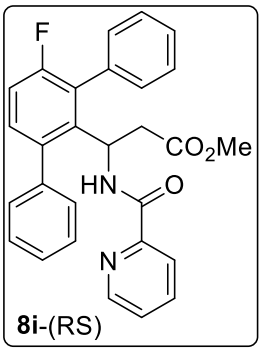
^1H NMR (400 MHz, $CDCl_3$): δ_H 8.45 (1H, d, J = 4.6 Hz), 8.04 (1H, d, J = 7.8 Hz), 7.80-7.76 (2H, m), 7.55-7.25 (8H, m), 7.16-7.12 (2H, m), 7.07 (1H, t, J = 8.4 Hz), 5.75-5.69 (1H, m), 3.46 (3H, s), 2.69 (1H, dd, J_1 = 15.3 Hz, J_2 = 10.0 Hz), 2.59 (1H, dd, J_1 = 15.3 Hz, J_2 = 4.9 Hz);

$^{13}C\{^1H\}$ NMR ($CDCl_3$, ~101 MHz): δ_C 169.8, 162.8, 159.5 (d, J_{C-F} = 243.3 Hz), 148.9, 147.8, 139.1, 138.7 (d, J_{C-F} = 1.1 Hz), 137.1, 136.8 (d, J_{C-F} = 3.7 Hz), 134.1, 133.6, 132.2 (d, J_{C-F} = 1.2 Hz), 132.1 (d, J_{C-F} = 8.5 Hz), 131.7, 131.2, 130.9, 128.9, 128.7, 128.5, 128.2 (d, J_{C-F} = 17.5 Hz), 126.2, 121.8, 114.2 (d, J_{C-F} = 23.1 Hz), 51.8, 47.9, 41.2;

^{19}F $\{^1H\}$ NMR (~376 MHz, $CDCl_3$): δ_F = -112.20.

HRMS (ESI): *m/z* $[M + Na]^+$ calcd for $C_{28}H_{21}Cl_2FN_2NaO_3$: 545.0811; found: 545.0820.

Methyl 3-(4'-fluoro-[1,1':3',1''-terphenyl]-2'-yl)-3-(picolinamido)propanoate (8i-(RS)):



The compound **8i**-(RS) was obtained through procedure F after purification by column chromatography on silica gel (EtOAc:hexanes = 50:50) as a yellow solid (36 mg, 53%, 0.15 mmol);

R_f (EtOAc/hexanes = 50:50) 0.60;

mp: 134-136 ^oC;

IR (DCM): 3346, 1685, 1587 cm^{-1};

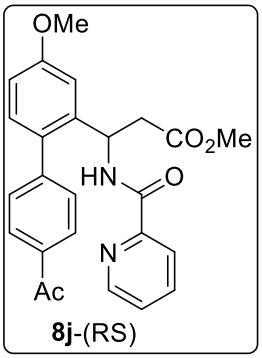
1H NMR (400 MHz, $CDCl_3$): δ_H 8.40 (1H, d, J = 4.3 Hz), 8.05 (1H, d, J = 7.8 Hz), 7.84 (1H, d, J = 8.4 Hz), 7.76 (1H, td, J_1 = 7.7 Hz, J_2 = 1.4 Hz), 7.57-7.52 (2H, m), 7.45-7.32 (7H, m), 7.27-7.25 (2H, m), 7.18-7.15 (1H, m), 7.07 (1H, t, J = 8.4 Hz), 5.79-5.73 (1H, m), 3.42 (3H, s), 2.69 (1H, dd, J_1 = 15.4 Hz, J_2 = 9.8 Hz), 2.61 (1H, dd, J_1 = 15.4 Hz, J_2 = 5.1 Hz);

$^{13}C\{^1H\}$ NMR ($CDCl_3$, ~101 MHz): δ_C 170.2, 162.8, 159.6 (d, J_{C-F} = 254.8 Hz), 149.2, 147.6, 140.9, 138.5 (d, J_{C-F} = 1.3 Hz), 138.1 (d, J_{C-F} = 3.6 Hz), 137.3, 134.0 (d, J_{C-F} = 1.0 Hz), 131.9 (d, J_{C-F} = 8.5 Hz), 130.4, 130.1, 129.7, 129.4 (d, J_{C-F} = 17.5 Hz), 128.6, 128.4, 128.3, 128.1, 127.5, 126.1, 122.1, 114.1 (d, J_{C-F} = 23.3 Hz), 51.8, 48.0, 41.1;

$^{19}F\{^{1}H\}$ NMR (~376 MHz, $CDCl_3$): δ_F = -113.09.

HRMS (ESI): *m/z* $[M + Na]^+$ calcd for $C_{28}H_{23}FN_2NaO_3$: 477.1590 found: 477.1593.

Methyl 3-(4'-acetyl-4-methoxy-[1,1'-biphenyl]-2-yl)-3-(picolinamido)propanoate (8j-(RS)): The compound **8j**-(RS) was obtained through procedure F after purification by column chromatography on silica gel (EtOAc:hexanes = 50:50) as a colourless solid (58 mg, 90%, 0.15 mmol);



8j-(RS)

R_f (EtOAc/hexanes = 50:50) 0.30;

mp: 78-80 °C;

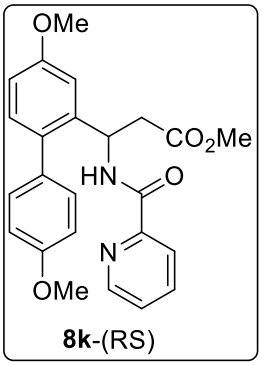
IR (DCM): 3368, 1677, 1512 cm^{-1};

^{1}H NMR (400 MHz, $CDCl_3$): δ_H 8.96 (1H, d, *J* = 7.9 Hz), 8.59 (1H, d, *J* = 4.8 Hz), 8.13 (1H, d, *J* = 7.8 Hz), 8.04 (2H, d, *J* = 8.4 Hz), 7.83 (1H, td, J_1 = 7.7 Hz, J_2 = 1.6 Hz), 7.59 (2H, d, *J* = 8.2 Hz), 7.46-7.42 (1H, m), 7.16 (1H, d, *J* = 8.4 Hz), 7.08 (1H, d, *J* = 2.5 Hz), 6.87 (1H, dd, J_1 = 8.4 Hz, J_2 = 2.6 Hz), 5.71-5.66 (1H, m), 3.82 (3H, s), 3.57 (3H, s), 2.77-2.67 (2H, m), 2.65 (3H, s);

$^{13}C\{^{1}H\}$ NMR ($CDCl_3$, ~76 MHz): δ_C 197.9, 171.0, 163.6, 159.7, 149.6, 148.3, 145.6, 139.7, 137.3, 135.8, 132.8, 131.5, 129.9, 128.5, 126.3, 122.2, 112.5, 112.1, 55.4, 51.8, 47.3, 39.9, 26.7;

HRMS (ESI): *m/z* $[M + Na]^+$ calcd for $C_{25}H_{24}N_2NaO_5$: 455.1583; found: 455.1582.

Methyl 3-(4,4'-dimethoxy-[1,1'-biphenyl]-2-yl)-3-(picolinamido)propanoate (8k-(RS)):



8k-(RS)

The compound **8k**-(RS) was obtained through procedure F after purification by column chromatography on silica gel (EtOAc:hexanes = 50:50) as a colourless solid (52 mg, 83%, 0.15 mmol);

R_f (EtOAc/hexanes = 50:50) 0.40;

mp: 140-142 °C;

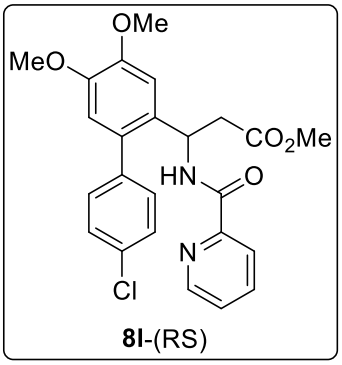
IR (DCM): 3376, 1679, 1505 cm^{-1};

^{1}H NMR (400 MHz, $CDCl_3$): δ_H 9.02 (1H, d, *J* = 7.9 Hz), 8.59 (1H, d, *J* = 4.5 Hz), 8.15 (1H, d, *J* = 7.8 Hz), 7.82 (1H, t, *J* = 7.6 Hz), 7.43-7.38 (3H, m), 7.14 (1H, d, *J* = 8.3 Hz), 7.04 (1H, s), 6.98 (2H, d, *J* = 8.0 Hz), 6.83 (1H, d, *J* = 8.4 Hz), 5.76-5.71 (1H, m), 3.85 (3H, s), 3.80 (3H, s), 3.57 (3H, s), 2.76-2.64 (2H, m);

$^{13}C\{^{1}H\}$ NMR ($CDCl_3$, ~101 MHz): δ_C 171.3, 163.6, 159.0, 158.7, 149.7, 148.3, 139.9, 137.3, 133.6, 132.8, 131.9, 130.6, 126.2, 122.2, 113.9, 112.2, 111.9, 55.3, 55.3, 51.8, 47.4, 39.8;

HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{24}H_{25}N_2O_5$: 421.1763 found: 421.1768.

Methyl 3-(4'-chloro-4,5-dimethoxy-[1,1'-biphenyl]-2-yl)-3-(picolinamido)propanoate (8l-(RS)): The compound **8l**-(RS) was obtained through procedure F after purification by column chromatography on silica gel (EtOAc:hexanes = 50:50) as a colourless solid (48 mg, 53%, 0.20 mmol);



R_f (EtOAc/hexanes = 50:50) 0.6;

mp: 138-140 ^oC;

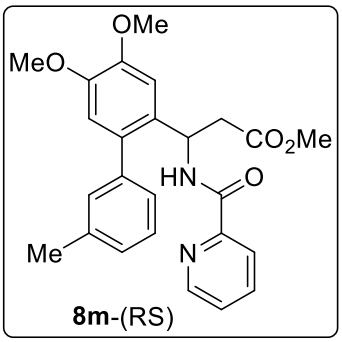
IR (DCM): 3370, 1734, 1672 cm^{-1};

^1H NMR (400 MHz, $CDCl_3$): δ_H 8.97 (1H, d, J = 7.8 Hz), 8.59 (1H, d, J = 4.7 Hz), 8.14 (1H, d, J = 7.8 Hz), 7.83 (1H, t, J = 7.7 Hz), 7.45-7.40 (5H, m), 7.02 (1H, s), 6.69 (1H, s), 5.60-5.55 (1H, m), 3.89 (3H, s), 3.85 (3H, s), 3.58 (3H, s), 2.79 (1H, dd, J_1 = 15.4 Hz, J_2 = 6.4 Hz), 2.71 (1H, dd, $J1$ = 15.4 Hz, J_2 = 6.2 Hz);

$^{13}C\{^1H\}$ NMR ($CDCl_3$, ~101 MHz): δ_C 171.3, 163.6, 149.7, 148.7, 148.3, 148.0, 139.0, 137.4, 133.3, 132.8, 130.9, 130.5, 128.6, 126.3, 122.2, 113.4, 109.0, 56.1, 55.9, 51.9, 47.3, 40.1;

HRMS (ESI): m/z $[M + Na]^+$ calcd for $C_{24}H_{23}ClN_2NaO_5$: 477.1193 found: 477.1197.

Methyl 3-(4,5-dimethoxy-3'-methyl-[1,1'-biphenyl]-2-yl)-3-(picolinamido)propanoate (8m-(RS)): The compound **8m**-(RS) was obtained through procedure F after purification by column chromatography on silica gel (EtOAc:hexanes = 50:50) as a yellow solid (60 mg, 69%, 0.20 mmol);



R_f (EtOAc/hexanes = 50:50) 0.60;

mp: 140-142 ^oC;

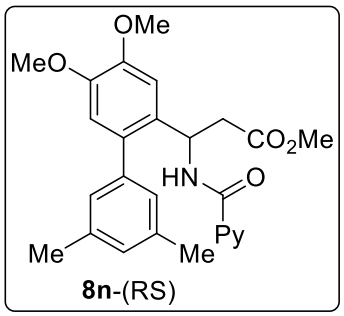
IR (DCM): 3374, 1753, 1673 cm^{-1};

^1H NMR (400 MHz, $CDCl_3$): δ_H 8.95 (1H, d, J = 7.9 Hz), 8.59 (1H, d, J = 4.5 Hz), 8.15 (1H, d, J = 7.8 Hz), 7.83 (1H, td, J_1 = 7.7 Hz, J_2 = 1.3 Hz), 7.44-7.41 (1H, m), 7.36-7.17 (4H, m), 7.03 (1H, s), 6.73 (1H, s), 5.67-5.62 (1H, m), 3.89 (3H, s), 3.85 (3H, s), 3.58 (3H, s), 2.80 (1H, dd, J_1 = 15.3 Hz, J_2 = 6.4 Hz), 2.72 (1H, dd, J_1 = 15.3 Hz, J_2 = 6.2 Hz), 2.39 (3H, s);

$^{13}C\{^1H\}$ NMR ($CDCl_3$, ~101 MHz): δ_C 171.4, 163.3, 149.7, 148.2, 147.7, 140.4, 137.9, 137.2, 134.2, 130.1, 130.1, 128.2, 127.9, 126.4, 126.1, 122.1, 113.5, 109.1, 56.0, 55.8, 51.7, 47.4, 39.9, 21.4;

HRMS (ESI): m/z $[M + Na]^+$ calcd for $C_{25}H_{26}N_2NaO_5$: 457.1739; found: 457.1745.

Methyl 3-(4,5-dimethoxy-3',5'-dimethyl-[1,1'-biphenyl]-2-yl)-3-(picolinamido)propanoate (8n-(RS)): The compound **8n**-(RS) was obtained through procedure F after purification by column chromatography on silica gel (EtOAc:hexanes = 50:50) as a colourless solid (58 mg, 65%, 0.20 mmol);



8n-(RS)

R_f (EtOAc/hexanes = 50:50) 0.60;

mp: 134-136 °C;

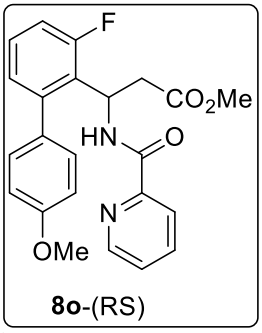
IR (DCM): 3378, 1736, 1513 cm^{-1};

^1H NMR (400 MHz, $CDCl_3$): δ_H 8.89 (1H, d, J = 8.0 Hz), 8.59 (1H, d, J = 4.6 Hz), 8.15 (1H, d, J = 7.8 Hz), 7.83 (1H, td, J_1 = 7.7 Hz, J_2 = 1.5 Hz), 7.44-7.40 (1H, m), 7.03 (3H, d, J = 8.0 Hz), 7.00 (1H, s), 6.72 (1H, s), 5.64 (1H, dd, J_1 = 14.3 Hz, J_2 = 6.4 Hz), 3.90 (3H, s), 3.84 (3H, s), 3.58 (3H, s), 2.82 (1H, dd, J_1 = 15.3 Hz, J_2 = 6.4 Hz), 2.73 (1H, dd, J_1 =15.3 Hz, J_2 =6.3 Hz), 2.35 (6H, s);

$^{13}C\{^1H\}$ NMR ($CDCl_3$, ~101 MHz): δ_C 171.4, 163.3, 149.8, 148.1, 148.0, 147.7, 140.4, 137.8, 137.2, 134.4, 130.1, 128.8, 127.2, 126.1, 122.1, 113.5, 109.3, 56.0, 55.8, 51.7, 47.6, 40.0, 21.3;

HRMS (ESI): *m/z* $[M + Na]^+$ calcd for $C_{26}H_{28}N_2NaO_5$: 471.1896; found: 471.1906.

Methyl 3-(3-fluoro-4'-methoxy-[1,1'-biphenyl]-2-yl)-3-(picolinamido)propanoate (8o-(RS)): The compound **8o**-(RS) was obtained through procedure F after purification by column chromatography on silica gel (EtOAc:hexanes = 50:50) as a brown solid (47 mg, 77%, 0.15 mmol);



8o-(RS)

R_f (EtOAc/hexanes = 50:50) 0.40;

mp: 128-130 °C;

IR (DCM): 3388, 1742, 1679 cm^{-1};

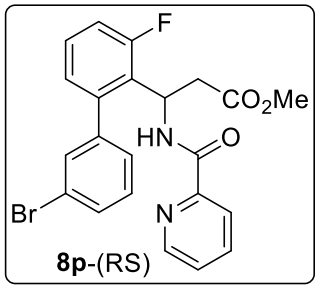
^1H NMR (400 MHz, $CDCl_3$): δ_H 8.84 (1H, d, J = 9.2 Hz), 8.57 (1H, d, J = 4.3 Hz), 8.15 (1H, d, J = 7.8 Hz), 7.80 (1H, td, J_1 = 7.7 Hz, J_2 = 1.6 Hz), 7.42-7.37 (3H, m), 7.30-7.24 (1H, m), 7.10-7.01 (4H, m), 5.95-5.89 (1H, m), 3.87 (3H, s), 3.52 (3H, s), 3.02 (1H, dd, J_1 = 14.8 Hz, J_2 = 8.3 Hz), 2.87 (1H, dd, J_1 = 14.8 Hz, J_2 = 6.7 Hz);

$^{13}C\{^1H\}$ NMR ($CDCl_3$, ~101 MHz): δ_C 170.5, 163.2, 162.2 (d, J_{C-F} = 243.5 Hz), 159.2, 149.7, 148.2, 143.6 (d, J_{C-F} = 4.6 Hz), 137.2, 131.9 (d, J_{C-F} = 2.3 Hz), 130.6, 128.8 (d, J_{C-F} = 10.0 Hz), 126.8, 126.2, 125.6 (d, J_{C-F} = 11.6 Hz), 122.3, 115.0 (d, J_{C-F} = 22.5 Hz), 113.8, 55.3, 51.8, 45.5, 40.1;

$^{19}F\{^1H\}$ NMR (~376 MHz, $CDCl_3$): δ_F = -115.52.

HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{23}H_{22}FN_2O_4$: 409.1564; found: 409.1552.

Methyl 3-(3'-bromo-3-fluoro-[1,1'-biphenyl]-2-yl)-3-(picolinamido)propanoate (8p-(RS)): The compound **8p**-(RS) was obtained through procedure F after purification by column chromatography on silica gel (EtOAc:hexanes = 50:50) as a yellow solid (85 mg, 74 %, 0.25 mmol);



R_f (EtOAc/hexanes = 50:50) 0.50;

mp: 90-92 °C;

IR (DCM): 3385, 1740, 1679 cm^{-1};

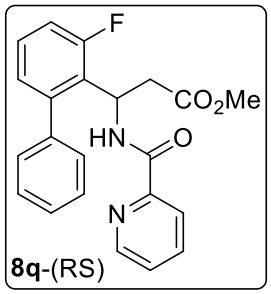
1H NMR (400 MHz, $CDCl_3$): δ_H 8.79 (1H, d, J = 9.0 Hz), 8.57 (1H, d, J = 4.3 Hz), 8.15 (1H, d, J = 7.8 Hz), 7.81 (1H, td, J_1 = 7.7 Hz, J_2 = 1.6 Hz), 7.56-7.47 (3H, m), 7.42-7.36 (2H, m), 7.32-7.27 (1H, m), 7.14-7.09 (1H, m), 7.03 (1H, d, J = 7.4 Hz), 5.85-5.79 (1H, m), 3.54 (3H, s), 3.02 (1H, dd, J_1 = 14.8 Hz, J_2 = 8.0 Hz), 2.91 (1H, dd, J_1 = 14.8 Hz, J_2 = 7.0 Hz);

$^{13}C\{^1H\}$ NMR ($CDCl_3$, ~101 MHz): δ_C 170.2, 162.0 (d, J_{C-F} = 244.3 Hz), 163.1, 149.5, 148.1, 142.2 (d, J_{C-F} = 4.9 Hz), 141.4 (d, J_{C-F} = 2.6 Hz) 137.2, 132.3, 130.8, 129.8, 129.0 (d, J_{C-F} = 10.0 Hz), 128.2, 126.3, 126.2, 125.5 (d, J_{C-F} = 12.2 Hz), 122.2, 122.2, 115.7 (d, J_{C-F} = 22.4 Hz), 51.8, 45.3, 40.0;

$^{19}F\{^1H\}$ NMR (~376 MHz, $CDCl_3$): δ_F = -115.01.

HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{22}H_{19}BrFN_2O_3$: 457.0563; found: 457.0569.

Methyl 3-(3-fluoro-[1,1'-biphenyl]-2-yl)-3-(picolinamido)propanoate (8q-(RS)): The compound **8q**-(RS) was obtained through procedure F after purification by column chromatography on silica gel (EtOAc:hexanes = 50:50) as a colourless solid (43 mg, 76%, 0.15 mmol);



R_f (EtOAc/hexanes = 50:50) 0.60;

mp: 120-122 °C;

IR (DCM): 3391, 1682, 1515 cm^{-1};

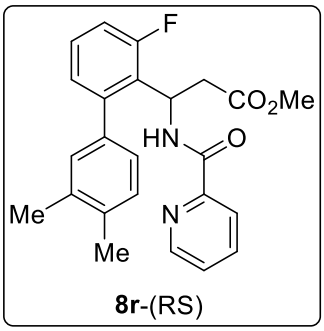
^1H NMR (400 MHz, $CDCl_3$): δ_H 8.83 (1H, d, J = 9.1 Hz), 8.57 (1H, d, J = 4.6 Hz), 8.15 (1H, d, J = 7.8 Hz), 7.81 (1H, td, J_1 = 7.7 Hz, J_2 = 1.6 Hz), 7.51-7.39 (6H, m), 7.32-7.26 (1H, m), 7.13-7.05 (2H, m), 5.90-5.84 (1H, m), 3.51 (3H, s), 3.01 (1H, dd, J_1 =14.8 Hz, J_2 = 8.2 Hz), 2.87 (1H, dd, J_1 = 14.8 Hz, J_2 = 6.7 Hz);

$^{13}C\{^1H\}$ NMR ($CDCl_3$, ~101 MHz): δ_H 170.4, 163.1, 162.1 (d, J_{C-F} = 243.9 Hz), 149.7, 148.2, 144.0 (d, J_{C-F} = 4.6 Hz), 139.5, 137.2, 129.4, 128.8 (d, J_{C-F} = 9.9 Hz), 128.4, 127.8, 126.5 (d, J_{C-F} = 2.2 Hz), 126.2, 125.5 (d, J_{C-F} = 11.8 Hz), 122.3, 115.2 (d, J_{C-F} = 22.5 Hz), 51.8, 45.5, 40.1;

$^{19}F\{^{1}H\}$ NMR (~376 MHz, $CDCl_3$): δ_F = -115.45.

HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{22}H_{20}FN_2O_3$: 379.1458; found: 379.1454.

Methyl 3-(3-fluoro-3',4'-dimethyl-[1,1'-biphenyl]-2-yl)-3-(picolinamido)propanoate (8r-(RS)): The compound **8r**-(RS) was obtained through procedure F after purification by column chromatography on silica gel (EtOAc:hexanes = 50:50) as a colourless solid (77 mg, 76%, 0.25 mmol);



8r-(RS)

R_f(EtOAc/hexanes = 50:50) 0.6;

mp: 105-107 °C;

IR (DCM): 3391, 1741, 1680 cm^{-1};

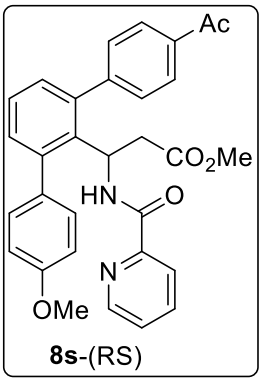
^{1}H NMR (400 MHz, $CDCl_3$): δ_H 8.80 (1H, d, *J* = 9.2 Hz), 8.56 (1H, d, *J* = 4.7 Hz), 8.14 (1H, d, *J* = 7.8 Hz), 7.79 (1H, td, J_1 = 7.7 Hz, J_2 = 1.0 Hz), 7.40-7.37 (1H, m), 7.29-7.24 (2H, m), 7.18-7.17 (2H, m), 7.09-7.04 (2H, m), 5.96-5.90 (1H, m), 3.52 (3H, s), 3.02 (1H, dd, J_1 = 14.7 Hz, J_2 = 8.3 Hz), 2.89 (1H, dd, J_1 = 14.8 Hz, J_2 = 6.6 Hz), 2.32 (6H, s);

$^{13}C\{^{1}H\}$ NMR ($CDCl_3$, ~101 MHz): δ_C 170.6, 163.1, 162.2 (d, J_{C-F} = 244.1 Hz), 149.8, 148.2, 144.1 (d, J_{C-F} = 4.6 Hz), 137.2, 137.1, 136.5, 136.1, 130.6, 129.7, 128.7 (d, J_{C-F} = 10.0 Hz), 126.7, 126.6 (d, J_{C-F} = 2.4 Hz), 126.1, 125.5 (d, J_{C-F} = 11.7 Hz), 122.3, 114.9 (d, J_{C-F} = 22.4 Hz), 51.8, 45.5, 40.2, 19.8, 19.6;

$^{19}F\{^{1}H\}$ NMR (~376 MHz, $CDCl_3$): δ_F = -115.54.

HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{24}H_{24}FN_2O_3$: 407.1771; found: 407.1768.

Methyl 3-(4-acetyl-4''-methoxy-[1,1':3',1''-terphenyl]-2'-yl)-3-(picolinamido)propanoate (8s-(RS)): The compound **8s**-(RS) was obtained through procedure F after purification by column chromatography on silica gel (EtOAc:hexanes = 30:70) as a colourless semi-solid (13 mg, 20%, 0.13 mmol scale);



8s-(RS)

R_f(EtOAc/hexanes = 30:70) 0.40;

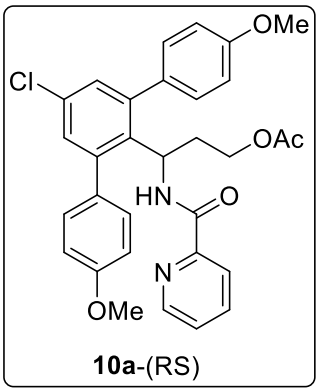
IR (DCM): 3386, 1679, 1516 cm^{-1};

^{1}H NMR (400 MHz, $CDCl_3$): δ_H 8.32-8.31 (1H, m), 7.99-7.84 (4H, m), 7.70 (1H, td, J_1 = 7.7 Hz, J_2 = 1.7 Hz), 7.46-7.19 (6H, m), 7.11 (1H, dd, J_1 = 7.6 Hz, J_2 = 1.5 Hz), 7.05 (1H, dd, J_1 = 7.6 Hz, J_2 = 1.5 Hz), 6.89-6.88 (2H, m), 5.81-5.75 (1H, m), 3.80 (3H, s), 3.36 (3H, s), 2.64 (1H, dd, J_1 = 15.3 Hz, J_2 = 9.7 Hz), 2.58 (3H, s), 2.54 (1H, dd, J_1 = 15.4 Hz, J_2 = 5.3 Hz);

$^{13}C\{^{1}H\}$ NMR (~101 MHz, $CDCl_3$): δ_C 197.9, 170.3, 162.8, 158.9, 149.4, 147.7, 147.1, 142.3, 141.3, 137.1, 136.1, 135.9, 133.8, 131.7, 130.6, 130.1, 129.8, 128.3, 126.7, 126.0, 122.0, 113.7, 55.3, 51.7, 47.9, 41.3, 26.7;

HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{31}H_{29}N_2O_5$: 509.2076; found: 509.2066.

3-(5''-Chloro-4,4''-dimethoxy-[1,1':3',1''-terphenyl]-2'-yl)-3-(picolinamido)propyl acetate (10a-(RS)): The compound **10a**-(RS) was obtained from procedure G after purification by column chromatography on silica gel (EtOAc:hexanes = 50:50) as a brown solid (65 mg, 60%, 0.20 mmol scale);



10a-(RS)

R_f (EtOAc/hexanes = 50:50) 0.4;

mp: 126-128 ^oC;

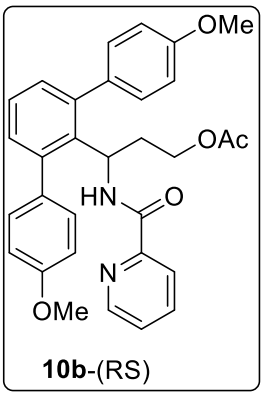
IR (DCM): 3374, 1739, 1513 cm^{-1};

^1H NMR (400 MHz, $CDCl_3$): δ_H 8.39-8.38 (1H, m), 8.06 (1H, dt, J_1 = 7.8 Hz, J_2 = 0.9 Hz), 7.78 (2H, td, J_1 = 7.7 Hz, J_2 = 1.7 Hz), 7.39-7.26 (5H, m), 7.13 (2H, s), 6.92 (4H, br. s), 5.58-5.52 (1H, m), 3.86 (6H, s), 3.82-3.75 (2H, m), 2.01-1.95 (2H, m), 1.77 (3H, s);

$^{13}C\{^{1}H\}$ NMR (~101 MHz, $CDCl_3$): δ_C 170.9, 163.2, 159.0, 149.5, 147.6, 143.6, 137.1, 136.4, 133.0, 131.5, 130.6, 126.0, 122.0, 113.7, 113.6, 61.2, 55.3, 47.6, 36.0, 20.7;

HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{31}H_{30}ClN_2O_5$: 545.1843; found: 545.1843.

3-(4,4''-Dimethoxy-[1,1':3',1''-terphenyl]-2'-yl)-3-(picolinamido)propyl acetate (10b-(RS)): The compound **10b**-(RS) was obtained from procedure G after purification by column chromatography on silica gel (EtOAc:hexanes = 50:50) as a brown solid (65 mg, 64%, 0.20 mmol scale);



10b-(RS)

R_f (EtOAc/hexanes = 50:50) 0.4;

mp: 138-140 ^oC;

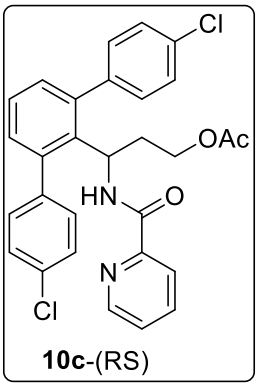
IR (DCM): 3372, 1736, 1511 cm^{-1};

^1H NMR (400 MHz, $CDCl_3$): δ_H 8.40-8.39 (1H, m), 8.07 (1H, d, J = 7.8 Hz), 7.85 (1H, d, J = 9.3 Hz), 7.77 (1H, td, J_1 = 7.7 Hz, J_2 = 1.7 Hz), 7.38-7.22 (6H, m), 7.12 (2H, d, J = 7.5 Hz), 6.94 (4H, br. s), 5.66-5.60 (1H, m), 3.86 (6H, s), 3.82-3.75 (2H, m), 2.07-1.93 (2H, m), 1.78 (3H, s);

$^{13}C\{^{1}H\}$ NMR (~101 MHz, $CDCl_3$): δ_C 170.9, 163.1, 158.7, 149.7, 147.5, 141.9, 137.5, 137.1, 134.3, 131.0, 130.8, 126.1, 125.9, 122.0, 113.5, 61.3, 55.3, 47.9, 36.2, 20.7;

HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{31}H_{31}N_2O_5$: 511.2233; found: 511.2229.

3-(4,4''-Dichloro-[1,1':3',1''-terphenyl]-2'-yl)-3-(picolinamido)propyl acetate (10c-(RS)):



The compound **10c**-(RS) was obtained from procedure G after purification by column chromatography on silica gel (EtOAc:hexanes = 50:50) as a colourless solid (66 mg, 64%, 0.20 mmol scale);

R_f (EtOAc/hexanes = 50:50) 0.6;

mp: 200-202 °C;

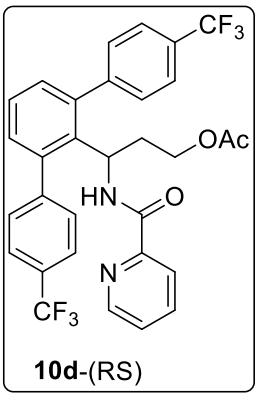
IR (DCM): 3372, 1737, 1513 cm^{-1};

^1H NMR (400 MHz, $CDCl_3$): δ_H 8.42 (1H, d, J = 4.5 Hz), 8.05 (1H, d, J = 7.8 Hz), 7.79 (1H, td, J_1 = 7.7 Hz, J_2 = 1.6 Hz), 7.68 (1H, d, J = 9.0 Hz), 7.54-7.11 (12H, m), 5.56-5.50 (1H, m), 3.84-3.75 (2H, m), 2.03-1.95 (2H, m), 1.79 (3H, s);

$^{13}C\{^1H\}$ NMR (~101 MHz, $CDCl_3$): δ_C 170.9, 163.2, 149.2, 147.8, 140.9, 140.3, 137.2, 137.2, 133.3, 130.9, 128.4, 126.4, 126.1, 121.8, 60.9, 47.9, 36.3, 20.7;

HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{29}H_{25}Cl_2N_2O_3$: 519.1242; found: 519.1250.

3-(4,4''-Bis(trifluoromethyl)-[1,1':3',1''-terphenyl]-2'-yl)-3-(picolinamido)propyl acetate (10d-(RS)): The compound **10d**-(RS) was obtained from procedure G after purification by column chromatography on silica gel (EtOAc:hexanes = 50:50) as a colourless solid (121 mg, 83%, 0.25 mmol scale);



R_f (EtOAc/hexanes = 50:50) 0.55;

mp: 172-174 °C;

IR (DCM): 3375, 1741, 1514 cm^{-1};

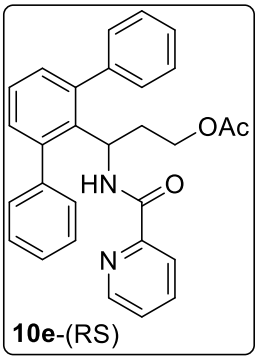
^1H NMR (400 MHz, $CDCl_3$): δ_H 8.30 (1H, d, J = 4.5 Hz), 8.05 (1H, d, J = 7.8 Hz), 7.81-7.30 (12H, m), 7.14 (2H, d, J = 7.6 Hz), 5.52-5.48 (1H, m), 3.84-3.78 (2H, m), 2.10-1.97 (2H, m), 1.71 (3H, s);

$^{13}C\{^1H\}$ NMR (~101 MHz, $CDCl_3$): δ_C 170.7, 163.3, 149.0, 147.7, 145.7, 140.7, 137.2, 136.9, 131.0, 130.0, 129.4 (q, J_{C-F} = 32.2 Hz), 126.5, 126.2, 125.2, 123.7 (q, J_{C-F} = 270.5 Hz), 121.8, 60.8, 48.1, 36.2, 20.5;

$^{19}F\{^1H\}$ NMR (~376 MHz, $CDCl_3$): δ_F = -62.35.

HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{31}H_{25}F_6N_2O_3$: 587.1769; found: 587.1780.

3-([1,1':3',1''-terphenyl]-2'-yl)-3-(picolinamido)propyl acetate (10e-(RS)): The compound



10e-(RS) was obtained from procedure G after purification by column chromatography on silica gel (EtOAc:hexanes = 50:50) as a colourless semi-solid (57 mg, 63%, 0.20 mmol scale);

R_f (EtOAc/hexanes = 50:50) 0.6;

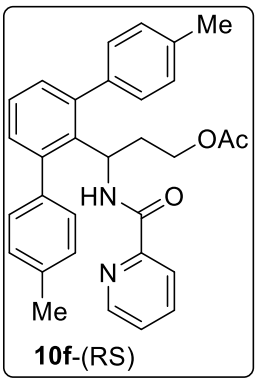
IR (DCM): 3371, 1736, 1515 cm^{-1};

^1H NMR (400 MHz, $CDCl_3$): δ_H 8.38-8.36 (1H, m), 8.06 (1H, d, J = 7.8 Hz), 7.80-7.74 (2H, m), 7.54-7.25 (12H, m), 7.15 (2H, d, J = 7.5 Hz), 5.62-5.57 (1H, m), 3.80-3.73 (2H, m), 2.05-1.97 (2H, m), 1.75 (3H, s);

$^{13}C\{^1H\}$ NMR (~101 MHz, $CDCl_3$): δ_C 170.9, 163.1, 149.6, 147.6, 142.2, 142.0, 137.0, 136.9, 130.8, 129.7, 128.1, 127.1, 126.1, 125.9, 122.0, 61.3, 48.0, 36.1, 20.8;

HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{29}H_{27}N_2O_3$: 451.2022; found: 451.2029.

3-(4,4''-Dimethyl-[1,1':3',1''-terphenyl]-2'-yl)-3-(picolinamido)propyl acetate (10f-(RS)):



The compound **10f**-(RS) was obtained from procedure G after purification by column chromatography on silica gel (EtOAc:hexanes = 50:50) as a brown solid (67 mg, 70%, 0.20 mmol scale);

R_f (EtOAc/hexanes = 50:50); 0.6

mp: 176-178 ^oC;

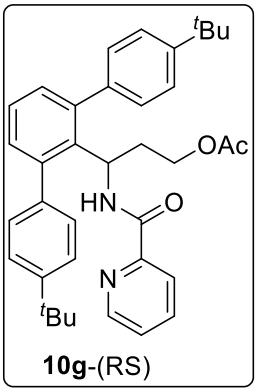
IR (DCM): 3306, 1738, 1513 cm^{-1};

^1H NMR (400 MHz, $CDCl_3$): δ_H 8.41 (1H, d, J = 4.6 Hz), 8.09 (1H, d, J = 7.8 Hz), 7.85 (1H, d, J = 9.2 Hz), 7.79 (1H, td, J_1 = 7.7 Hz, J_2 = 1.6 Hz), 7.40-7.14 (12H, m), 5.64 (1H, td, J_1 = 9.6 Hz, J_2 = 5.0 Hz), 3.84-3.77 (2H, m), 2.45 (6H, s), 2.12-2.00 (2H, m), 1.79 (3H, s);

$^{13}C\{^1H\}$ NMR (~101 MHz, $CDCl_3$): δ_C 170.9, 163.1, 149.8, 147.5, 142.2, 139.1, 137.1, 137.0, 136.6, 130.7, 129.5, 128.8, 126.1, 125.8, 122.0, 61.3, 47.9, 36.2, 21.3, 20.7;

HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{31}H_{31}N_2O_3$: 479.2335; found: 479.2328.

3-(4,4''-Di-tert-butyl-[1,1':3',1''-terphenyl]-2'-yl)-3-(picolinamido)propyl acetate (10g-(RS)): The compound **10g**-(RS) was obtained from procedure G after purification by column chromatography on silica gel (EtOAc:hexanes = 40:60) as a brown semi-solid (64 mg, 57%, 0.20 mmol scale);



10g-(RS)

R_f (EtOAc/hexanes = 40:60) 0.8;

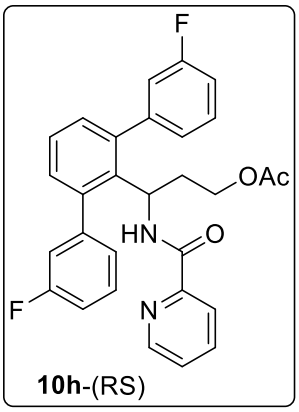
IR (DCM): 3375, 1739, 1511 cm^{-1};

^1H NMR (400 MHz, $CDCl_3$): δ_H 8.36 (1H, d, J = 4.2 Hz), 8.09 (1H, d, J = 7.8 Hz), 7.81-7.75 (2H, m), 7.47-7.34 (7H, m), 7.26-7.22 (3H, m), 7.12 (2H, d, J = 7.4 Hz), 5.66-5.60 (1H, m), 3.80-3.75 (2H, m), 2.08-2.02 (2H, m), 1.75 (3H, s), 1.38 (18H, s);

$^{13}C\{^1H\}$ NMR (~101 MHz, $CDCl_3$): δ_C 170.9, 163.2, 149.8, 149.7, 147.6, 142.2, 139.0, 137.0, 136.9, 130.9, 129.4, 126.1, 125.9, 124.9, 122.1, 61.4, 48.3, 36.1, 34.6, 31.5, 20.9;

HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{37}H_{43}N_2O_3$: 563.3274; found: 563.3274.

3-(3, 3''-Difluoro-[1,1':3',1''-terphenyl]-2'-yl)-3-(picolinamido)propyl acetate (10h-(RS)):



10h-(RS)

The compound **10h**-(RS) was obtained from procedure G after purification by column chromatography on silica gel (EtOAc:hexanes = 50:50) as a brown semi-solid (72 mg, 74%, 0.20 mmol scale);

R_f (EtOAc/hexanes = 50:50) 0.6;

IR (DCM): 3375, 1737, 1511 cm^{-1};

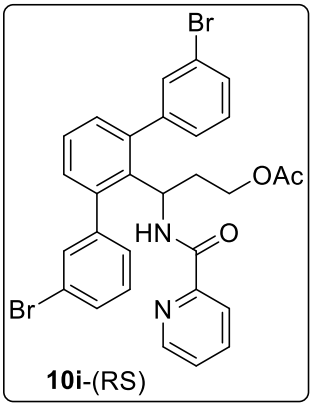
^1H NMR (400 MHz, $CDCl_3$): δ_H 8.40 (1H, d, J = 4.0 Hz), 8.07 (1H, d, J = 7.8 Hz), 7.83-7.75 (2H, m), 7.38-7.26 (6H, m), 7.15-7.07 (6H, m), 5.59-5.53 (1H, m), 3.84-3.75 (2H, m), 2.08- 1.95 (2H, m), 1.79 (3H, s);

$^{13}C\{^1H\}$ NMR (~101 MHz, $CDCl_3$): δ_C 170.8, 163.1, 162.3 (d, J_{C-F} = 245.4 Hz), 149.2, 147.7, 143.8 (d, J_{C-F} = 7.5 Hz), 140.8, 137.1, 136.8, 130.8, 129.6 (d, J_{C-F} = 8.4 Hz), 126.3, 125.9, 125.5 (d, J_{C-F} = 2.5 Hz), 121.9, 116.9 (d, J_{C-F} = 21.4 Hz), 114.1 (d, J_{C-F} = 20.7 Hz), 61.0, 47.8, 35.9, 20.5;

$^{19}F\{^1H\}$ NMR (~376 MHz, $CDCl_3$): δ_F = -112.56, -113.07, -114.71.

HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{29}H_{25}F_2N_2O_3$: 487.1833; found: 487.1827.

3-(3,3''-Dibromo-[1,1':3',1''-terphenyl]-2'-yl)-3-(picolinamido)propyl acetate (10i-(RS)):



The compound **10i**-(RS) was obtained from procedure G after purification by column chromatography on silica gel (EtOAc:hexanes = 50:50) as a colourless semi-solid (68 mg, 56%, 0.20 mmol scale);

R_f (EtOAc/hexanes = 50:50) 0.65;

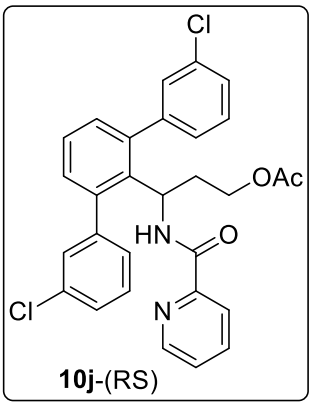
IR (DCM): 3375, 1740, 1514 cm^{-1};

^1H NMR (400 MHz, $CDCl_3$): δ_H 8.46 (1H, br. s), 8.08 (1H, d, J = 7.8 Hz), 7.81-7.76 (2H, m), 7.53-7.12 (12H, m), 5.54-5.48 (1H, m), 3.83-3.80 (2H, m), 2.08-1.95 (2H, m), 1.80 (3H, s);

$^{13}C\{^1H\}$ NMR (~101 MHz, $CDCl_3$): δ_C 170.9, 163.3, 149.2, 148.2, 143.9, 140.7, 137.1, 136.9, 132.6, 131.0, 130.3, 129.6, 128.3, 126.4, 126.0, 122.0, 122.0, 61.0, 48.0, 36.1, 20.7;

HRMS (ESI): *m/z* $[M + Na]^+$ calcd for $C_{29}H_{24}Br_2N_2NaO_3$: 629.0051; found: 629.0054.

3-(3,3''-Dichloro-[1,1':3',1''-terphenyl]-2'-yl)-3-(picolinamido)propyl acetate (10j-(RS)):



The compound **10j**-(RS) was obtained from procedure G after purification by column chromatography on silica gel (EtOAc:hexanes = 50:50) as a colourless semi-solid (55 mg, 53%, 0.20 mmol scale);

R_f (EtOAc/hexanes = 50:50); 0.6

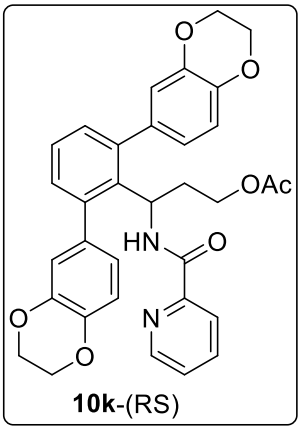
IR (DCM): 3373, 1739, 1512 cm^{-1};

^1H NMR (400 MHz, $CDCl_3$): δ_H 8.46 (1H, br. s), 8.10 (1H, d, J = 7.8 Hz), 7.82-7.78 (2H, m), 7.55-7.28 (10H, m), 7.15 (2H, d, J = 7.6 Hz), 5.57-5.51 (1H, m), 3.86-3.82 (2H, m), 2.07-1.99 (2H, m), 1.82 (3H, s);

$^{13}C\{^1H\}$ NMR (~101 MHz, $CDCl_3$): δ_C 170.9, 163.3, 149.3, 148.0, 143.6, 140.8, 137.1, 136.9, 134.1, 131.0, 129.8, 129.4, 127.9, 127.4, 126.4, 126.0, 122.0, 61.0, 48.1, 36.0, 20.7;

HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{29}H_{25}Cl_2N_2O_3$: 519.1242; found: 519.1233.

3-(2,6-Bis(2,3-dihydrobenzo[*b*][1,4]dioxin-6-yl)phenyl)-3-(picolinamido)propyl acetate



10k-(RS)

(10k-(RS)): The compound **10k**-(RS) was obtained from procedure G after purification by column chromatography on silica gel (EtOAc:hexanes = 50:50) as a brown solid (80 mg, 71%, 0.20 mmol scale);

R_f (EtOAc/hexanes = 50:50) 0.3;

mp: 108-110 ^oC;

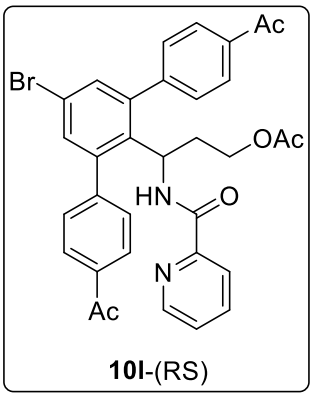
IR (DCM): 3366, 1736, 1506 cm^{-1};

^1H NMR (400 MHz, $CDCl_3$): δ_H 8.44 (1H, d, J = 4.5 Hz), 8.08 (1H, d, J = 7.8 Hz), 7.99 (1H, d, J = 8.7 Hz), 7.77 (1H, td, J_1 = 7.7 Hz, J_2 = 1.6 Hz), 7.38-7.34 (1H, m), 7.22 (1H, t, J = 7.6 Hz), 7.11 (2H, d, J = 7.4 Hz), 6.97-6.83 (6H, m), 5.68-5.65 (1H, m), 4.31 (8H, br. s), 3.84-3.81 (2H, m), 2.08-2.02 (2H, m), 1.85 (3H, s);

$^{13}C\{^1H\}$ NMR (~101 MHz, $CDCl_3$): δ_C 170.9, 163.1, 149.8, 147.7, 143.0, 142.8, 141.6, 137.2, 137.1, 135.3, 130.9, 126.1, 125.8, 123.0, 122.1, 118.7, 116.9, 64.4, 61.5, 47.9, 36.1, 20.8;

HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{33}H_{31}N_2O_7$: 567.2131; found: 567.2114.

3-(4,4''-Diacetyl-5'-bromo-[1,1':3',1''-terphenyl]-2'-yl)-3-(picolinamido)propyl acetate



10l-(RS)

(10l-(RS)): The compound **10l**-(RS) was obtained from procedure G after purification by column chromatography on silica gel (EtOAc:hexanes = 50:50) as a colourless solid (51 mg, 56%, 0.15 mmol scale);

R_f (EtOAc/hexanes = 50:50) 0.3;

mp: 112-114 ^oC;

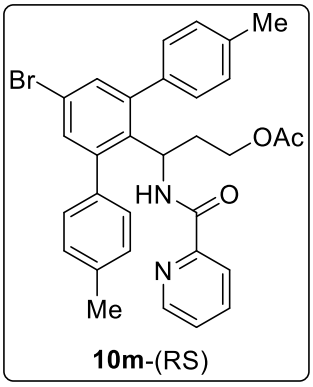
IR (DCM): 3373, 1738, 1514 cm^{-1};

^1H NMR (400 MHz, $CDCl_3$): δ_H 8.27 (1H, d, J = 4.2 Hz), 8.08-7.61 (9H, m), 7.43-7.27 (3H, m), 7.31 (2 H, s), 5.41-5.35 (1H, m), 3.82-3.72 (2H, m), 2.66 (6H, s), 2.08-1.95 (2H, m), 1.70 (3H, s);

$^{13}C\{^1H\}$ NMR (~101 MHz, $CDCl_3$): δ_C 197.6, 170.6, 163.0, 148.8, 147.4, 145.3, 143.0, 137.6, 136.3, 136.1, 133.3, 129.7, 128.4, 126.4, 122.1, 120.1, 60.9, 48.1, 35.8, 26.7, 20.6;

HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{33}H_{30}BrN_2O_5$: 613.1338; found: 613.1355.

3-(5'-Bromo-4,4''-dimethyl-[1,1':3',1''-terphenyl]-2'-yl)-3-(picolinamido)propyl acetate



10m-(RS)

(10m-(RS)): The compound **10m**-(RS) was obtained from procedure G after purification by column chromatography on silica gel (EtOAc:hexanes = 50:50) as a colourless solid (47 mg, 57%, 0.15 mmol scale);

R_f (EtOAc/hexanes = 50:50) 0.6;

mp: 142-144 ^{o}C;

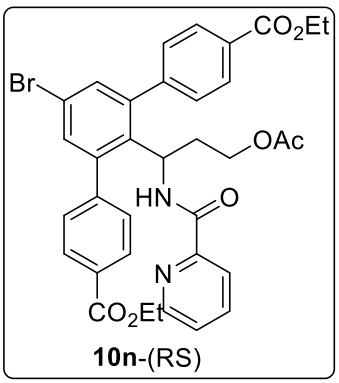
IR (DCM): 3371, 1738, 1511 cm^{-1};

^{1}H NMR (400 MHz, $CDCl_3$): δ_H 8.37-8.36 (1H, m), 8.06 (1H, d, J = 7.8 Hz), 7.79-7.72 (2H, m) 7.38-7.35 (2H, m), 7.28-7.07 (7H, m), 7.28 (2H, s), 5.54-5.48 (1H, m), 3.82-3.70 (2H, m), 2.41 (6H, s), 2.01-1.95 (2H, m), 1.75 (3H, s);

^{13}C{^{1}H} NMR (~101 MHz, $CDCl_3$): δ_C 170.8, 163.2, 149.5, 147.5, 144.1, 137.7, 137.2, 137.1, 136.5, 133.3, 129.3, 128.9, 125.9, 122.0, 119.7, 61.1, 47.7, 35.9, 21.3, 20.7;

HRMS (ESI): *m/z* [M + H]$^{+}$ calcd for $C_{31}H_{30}BrN_2O_3$: 557.1440; found: 557.1432.

Diethyl 2'-(3-acetoxy-1-(picolinamido)propyl)-5'-bromo-[1,1':3',1''-terphenyl]-4,4''-dicarboxylate (10n-(RS)): The compound **10n**-(RS) was obtained from procedure G after purification by column chromatography on silica gel (EtOAc:hexanes = 50:50) as a colourless semi-solid (23 mg, 34%, 0.10 mmol scale);



10n-(RS)

R_f (EtOAc/hexanes = 50:50) 0.3;

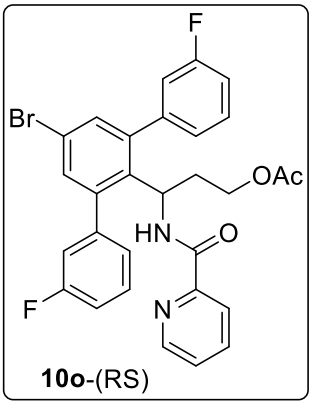
IR (DCM): 3368, 1719, 1515 cm^{-1};

^{1}H NMR (400 MHz, $CDCl_3$): δ_H 8.29-8.28 (1H, m), 8.17-7.56 (9H, m), 7.39-7.36 (1H, m), 7.32-7.27 (2H, m), 7.32 (2H, s), 5.40 (1H, td, J_1 = 10.2 Hz, J_2 = 4.5 Hz), 4.43 (4H, q, J = 7.1 Hz), 3.81-3.68 (2H, m), 2.05-1.88 (2H, m), 1.72 (3H, s), 1.43 (6H, t, J = 7.1 Hz);

^{13}C{^{1}H} NMR (~101 MHz, $CDCl_3$): δ_C 170.7, 166.3, 163.2, 149.0, 147.7, 145.0, 143.1, 137.2, 136.2, 133.2, 129.8, 129.6, 129.5, 126.2, 121.9, 120.1, 61.1, 60.9, 47.8, 35.9, 20.6, 14.4;

HRMS (ESI): *m/z* [M + H]$^{+}$ calcd for $C_{35}H_{34}BrN_2O_7$: 673.1549; found: 673.1555.

3-(5'-Bromo-3,3''-difluoro-[1,1':3',1''-terphenyl]-2'-yl)-3-(picolinamido)propyl acetate



10o-(RS)

(10o-(RS)): The compound **10o**-(RS) was obtained from procedure G after purification by column chromatography on silica gel (EtOAc:hexanes = 50:50) as a brown semi-solid (58 mg, 68%, 0.15 mmol scale);

R_f (EtOAc/hexanes = 50:50) 0.6;

IR (DCM): 3376, 1739, 1513 cm^{-1};

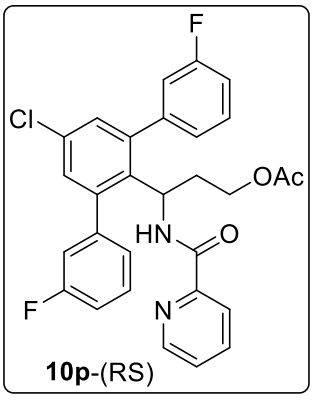
^1H NMR (400 MHz, $CDCl_3$): δ_H 8.39 (1H, d, J = 3.9 Hz), 8.06 (1H, d, J = 7.8 Hz), 7.79 (1H, td, J_1 = 7.7 Hz, J_2 = 1.5 Hz), 7.74 (1H, d, J = 8.5 Hz), 7.46-7.26 (8H, m), 7.13-7.08 (3H, m), 5.48-5.43 (1H, m), 3.83-3.77 (2H, m), 2.02-1.96 (2H, m), 1.79 (3H, s);

$^{13}C\{^1H\}$ NMR (~101 MHz, $CDCl_3$): δ_C 170.8, 163.3, 162.4 (d, J_{C-F} = 246.2 Hz), 149.1, 147.8, 142.7, 142.4 (d, J_{C-F} = 7.7 Hz), 137.2, 136.3, 133.5, 129.8 (d, J_{C-F} = 8.3 Hz), 126.2, 125.3 (d, J_{C-F} = 2.2 Hz), 122.0, 120.0, 116.8 (d, J_{C-F} = 21.6 Hz), 114.7 (d, J_{C-F} = 20.7 Hz), 60.9, 47.7, 35.8, 20.6;

$^{19}F\{^1H\}$ NMR (~376 MHz, $CDCl_3$): δ_F = -112.09, -112.64, -114.31.

HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{29}H_{24}BrF_2N_2O_3$: 565.0938; found: 565.0941.

3-(5'-Chloro-3,3''-difluoro-[1,1':3',1''-terphenyl]-2'-yl)-3-(picolinamido)propyl acetate



10p-(RS)

(10p-(RS)): The compound **10p**-(RS) was obtained from procedure G after purification by column chromatography on silica gel (EtOAc:hexanes = 50:50) as a brown semi-solid (45 mg, 58%, 0.15 mmol scale);

R_f (EtOAc/hexanes = 50:50) 0.6;

IR (DCM): 3376, 1738, 1512 cm^{-1};

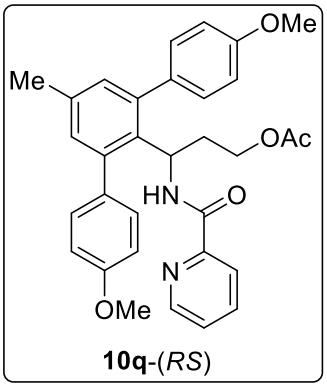
^1H NMR (400 MHz, $CDCl_3$): δ_H 8.39 (1H, d, J = 4.2 Hz), 8.08 (1H, d, J = 7.8 Hz), 7.82-7.75 (2H, m), 7.41-7.38 (4H, m), 7.16-7.08 (5H, m), 7.16 (2H, s), 5.50-5.44 (1H, m), 3.85-3.75 (2H, m), 2.03-1.97 (2H, m), 1.79 (3H, s);

$^{13}C\{^1H\}$ NMR (~101 MHz, $CDCl_3$): δ_C 170.8, 163.2, 162.4 (d, J_{C-F} = 246.3 Hz), 149.0, 147.7, 142.6, 142.5, 137.4, 135.8, 131.9, 130.6, 129.8 (d, J_{C-F} = 8.3 Hz), 126.2, 125.3 (d, J_{C-F} = 2.5 Hz), 122.1, 116.8 (d, J_{C-F} = 21.7 Hz), 114.7 (d, J_{C-F} = 20.8 Hz), 61.0, 47.6, 35.8, 20.6;

$^{19}F\{^1H\}$ NMR (~376 MHz, $CDCl_3$): δ_F = -112.12, -112.65, -114.32.

HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{29}H_{24}ClF_2N_2O_3$: 521.1444; found: 521.1446.

3-(4,4''-Dimethoxy-5'-methyl-[1,1':3',1''-terphenyl]-2'-yl)-3-(picolinamido)propyl acetate (10q-(RS)): The compound **10q**-(RS) was obtained from procedure G after purification by column chromatography on silica gel (EtOAc:hexanes = 50:50) as a brown semi-solid (37 mg, 47%, 0.15 mmol scale);



10q-(*RS*)

R_f (EtOAc/hexanes = 50:50) 0.7;

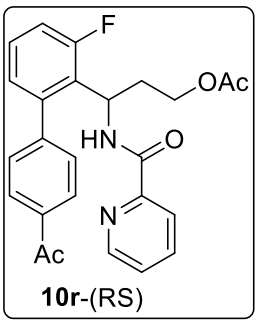
IR (DCM): 3371, 1736, 1510 cm^{-1};

^1H NMR (400 MHz, $CDCl_3$): δ_H 8.40 (1H, d, J = 4.6 Hz), 8.07 (1H, d, J = 7.8 Hz), 7.85 (1H, d, J = 9.3 Hz), 7.77 (1H, td, J_1 = 7.7 Hz, J_2 = 1.7 Hz), 7.37-7.26 (5H, m), 6.95 (6H, br. s), 5.59 (1H, td, J_1 = 7.7 Hz, J_2 = 5.3 Hz), 3.86 (6H, s), 3.80-3.74 (2H, m), 2.31 (3H, s), 2.02-1.95 (2H, m), 1.78 (3H, s);

$^{13}C\{^1H\}$ NMR (~101 MHz, $CDCl_3$): δ_C 171.0, 163.1, 158.6, 149.8, 147.5, 141.8, 137.1, 135.6, 134.5, 134.5, 131.7, 130.7, 125.8, 122.0, 113.4, 61.4, 55.3, 47.7, 36.2, 20.8, 20.7;

HRMS (ESI): *m/z* $[M + Na]^+$ calcd for $C_{32}H_{32}N_2NaO_5$: 547.2209; found: 547.2215.

3-(4'-Acetyl-3-fluoro-[1,1'-biphenyl]-2-yl)-3-(picolinamido)propyl acetate (10r-(RS)):



10r-(RS)

The compound **10r**-(RS) was obtained from procedure G after purification by column chromatography on silica gel (EtOAc:hexanes = 50:50) as a brown semi-solid (50 mg, 58%, 0.20 mmol scale);

R_f (EtOAc/hexanes = 50:50) 0.3;

IR (DCM): 3392, 1738, 1516 cm^{-1};

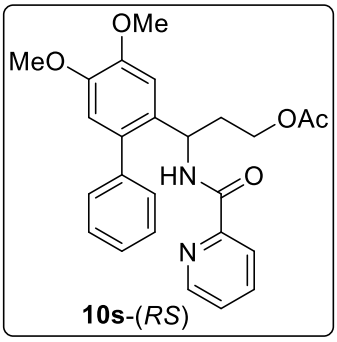
^1H NMR (400 MHz, $CDCl_3$): δ_H 8.82 (1H, d, J = 9.5 Hz), 8.58-8.57 (1H, m), 8.15 (1H, dt, J_1 = 7.8 Hz, J_2 = 1.0 Hz), 8.10 (2H, d, J = 8.6 Hz), 7.83 (1H, td, J_1 = 7.7 Hz, J_2 = 1.7 Hz), 7.62 (2H, br. s), 7.44-7.41 (1H, m), 7.34-7.28 (1H, m), 7.16-7.11 (1H, m), 7.04 (1H, dd, J_1 = 7.6 Hz, J_2 = 1.1 Hz), 5.57-5.50 (1H, m), 4.00-3.94 (1H, m), 3.90-3.86 (1H, m), 2.66 (3H, s), 2.30-2.25 (1H, m), 2.22-2.17 (1H, m), 1.76 (3H, s);

$^{13}C\{^1H\}$ NMR (~101 MHz, $CDCl_3$): δ_C 197.8, 170.8, 163.5, 162.2 (d, J_{C-F} = 244.1 Hz), 149.6, 148.2, 144.5 (d, J_{C-F} = 2.3 Hz), 142.6 (d, J_{C-F} = 5.0 Hz), 137.3, 136.2, 129.9, 128.8 (d, J_{C-F} = 9.8 Hz), 128.4, 126.3 (d, J_{C-F} = 12.0 Hz), 126.3, 126.1, 122.3, 115.9 (d, J_{C-F} = 22.4 Hz), 61.2, 45.7, 34.3, 26.7, 20.6;

$^{19}F\{^1H\}$ NMR (~376 MHz, $CDCl_3$): δ_F = -115.36.

HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{25}H_{24}FN_2O_4$: 435.1720; found: 435.1729.

3-(4,5-Dimethoxy-[1,1'-biphenyl]-2-yl)-3-(picolinamido)propyl acetate (10s-(RS)): The



10s-(*RS*)

compound **10s**-(RS) was obtained from procedure G after purification by column chromatography on silica gel (EtOAc:hexanes = 50:50) as a colourless semi-solid (45 mg, 69%, 0.15 mmol scale);

R_f (EtOAc/hexanes = 50:50) 0.5;

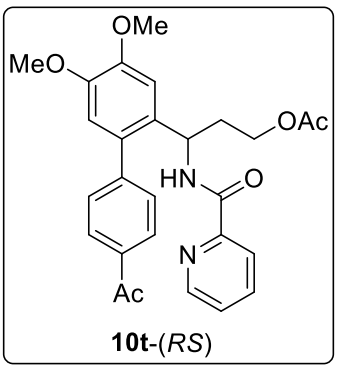
IR (DCM): 3368, 1736, 1514 cm^{-1};

^1H NMR (400 MHz, $CDCl_3$): δ_H 8.67 (1H, d, J = 5.5 Hz), 8.56 (1H, dd, J_1 = 4.8 Hz, J_2 = 0.6 Hz), 8.21 (1H, d, J = 7.8 Hz), 7.89 (1H, t, J = 7.6 Hz), 7.51-7.38 (5H, m), 7.38-7.34 (1H, m), 7.00 (1H, s), 6.74 (1H, s), 5.43-5.37 (1H, m), 3.99-3.86 (2H, m), 3.91 (3H, s), 3.85 (3H, s), 2.15-1.99 (2H, m), 1.88 (3H, s);

$^{13}C\{^1H\}$ NMR (~101 MHz, $CDCl_3$): δ_C 170.8, 163.3, 149.7, 148.7, 147.9, 147.7, 140.7, 137.8, 134.2, 131.2, 129.7, 128.3, 127.1, 126.3, 122.5, 113.5, 108.8, 61.4, 56.2, 56.0, 48.3, 35.4, 20.8;

HRMS (ESI): *m/z* $[M + Na]^+$ calcd for $C_{25}H_{26}N_2NaO_5$: 457.1739; found: 457.1729.

3-(4'-Acetyl-4,5-dimethoxy-[1,1'-biphenyl]-2-yl)-3-(picolinamido)propyl acetate (10t-(RS)): The compound **10t**-(RS) was obtained from procedure G after purification by column chromatography on silica gel (EtOAc:hexanes = 50:50) as a brown semi-solid (50 mg, 70%, 0.15 mmol scale);



10t-(*RS*)

R_f (EtOAc/hexanes = 50:50) 0.2;

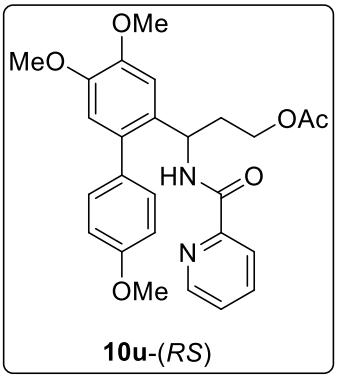
IR (DCM): 3346, 1736, 1605 cm^{-1};

^1H NMR (400 MHz, $CDCl_3$): δ_H 8.66 (1H, d, J = 7.6 Hz), 8.57 (1H, d, J = 4.2 Hz), 8.19 (1H, d, J = 7.8 Hz), 8.05 (2H, d, J = 8.5 Hz), 7.89 (1H, td, J_1 = 7.7 Hz, J_2 = 1.5 Hz), 7.64 (2H, d, J = 8.0 Hz), 7.48 (1H, td, J_1 = 5.5 Hz, J_2 = 0.6 Hz), 7.00 (1H, s), 6.72 (1H, s), 5.39-5.33 (1H, m), 3.99-3.88 (2H, m), 3.92 (3H, s), 3.86 (3H, s), 2.65 (3H, s), 2.17-2.00 (2H, m), 1.86 (3H, s);

$^{13}C\{^1H\}$ NMR (~101 MHz, $CDCl_3$): δ_C 197.8, 170.7, 163.3, 149.4, 149.2, 148.0, 147.7, 145.8, 137.9, 135.8, 132.8, 131.2, 130.1, 128.4, 126.5, 122.5, 113.0, 108.8, 61.4, 56.2, 56.0, 48.2, 35.5, 26.7, 20.7;

HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{27}H_{29}N_2O_6$: 477.2026; found: 477.2010.

3-(Picolinamido)-3-(4,4',5-trimethoxy-[1,1'-biphenyl]-2-yl)propyl acetate (10u-(RS)): The compound **10u**-(RS) was obtained from procedure G after purification by column chromatography on silica gel (EtOAc:hexanes = 50:50) as a brown semi-solid (53 mg, 76%, 0.15 mmol scale);



10u-(*RS*)

R_f (EtOAc/hexanes = 50:50) 0.3;

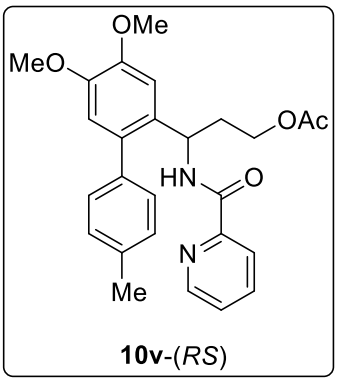
IR (DCM): 3373, 1736, 1505 cm^{-1};

^1H NMR (400 MHz, $CDCl_3$): δ_H 8.59 (1H, d, J = 7.6 Hz), 8.56 (1H, d, J = 4.6 Hz), 8.18 (1H, d, J = 7.8 Hz), 7.86 (1H, t, J = 7.6 Hz), 7.46-7.41 (3H, m), 6.99 (2H, d, J = 8.6 Hz), 6.95 (1H, s), 6.73 (1H, s), 5.44-5.38 (1H, m), 3.97-3.93 (2H, m), 3.90 (3H, s), 3.85 (6H, s), 2.14-1.94 (2H, m), 1.90 (3H, s);

$^{13}C\{^1H\}$ NMR (~101 MHz, $CDCl_3$): δ_C 170.8, 163.4, 158.7, 149.8, 148.5, 147.9, 147.8, 137.6, 133.8, 133.0, 131.4, 130.8, 126.3, 122.3, 113.7, 113.7, 108.8, 61.5, 56.2, 55.9, 55.3, 48.3, 35.5, 20.8;

HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{26}H_{29}N_2O_6$: 465.2026; found: 465.2029.

3-(4,5-Dimethoxy-4'-methyl-[1,1'-biphenyl]-2-yl)-3-(picolinamido)propyl acetate (10v-(RS)): The compound **10v**-(RS) was obtained from procedure G after purification by column chromatography on silica gel (EtOAc:hexanes = 50:50) as a colourless solid (38 mg, 56%, 0.15 mmol scale);



10v-(*RS*)

R_f (EtOAc/hexanes = 50:50) 0.4;

mp: 136-138 ^oC;

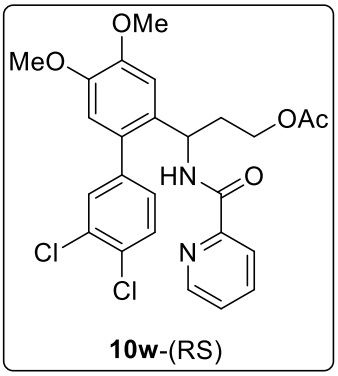
IR (DCM): 3343, 1737, 1507 cm^{-1};

^1H NMR (400 MHz, $CDCl_3$): δ_H 8.58-8.55 (2H, m), 8.19 (1H, d, J = 7.8 Hz), 7.86 (1H, td, J_1 = 7.7 Hz, J_2 = 1.6 Hz), 7.47-7.44 (1H, m), 7.39 (2H, d, J = 7.7 Hz), 7.27 (2H, d, J = 8.3 Hz), 6.96 (1H, s), 6.75 (1H, s), 5.44-5.39 (1H, m), 3.98-3.94 (2H, m), 3.92, (3H, s), 3.86 (3H, s), 2.42 (3H, s), 2.15-2.00 (2H, m), 1.91 (3H, s);

$^{13}C\{^1H\}$ NMR (~101 MHz, $CDCl_3$): δ_C 170.8, 163.5, 149.9, 148.5, 148.0, 147.8, 137.7, 137.4, 136.7, 134.2, 131.2, 129.5, 129.0, 126.2, 122.2, 113.6, 108.8, 61.5, 56.2, 55.9, 48.3, 35.4, 21.2, 20.7;

HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{26}H_{29}N_2O_5$: 449.2076; found: 449.2097.

3-(3',4'-Dichloro-4,5-dimethoxy-[1,1'-biphenyl]-2-yl)-3-(picolinamido)propyl acetate



(10w-(RS)): The compound **10w**-(RS) was obtained from procedure G after purification by column chromatography on silica gel (EtOAc:hexanes = 50:50) as a brown semi-solid (46 mg, 61%, 0.15 mmol scale);

R_f (EtOAc/hexanes = 50:50) 0.4;

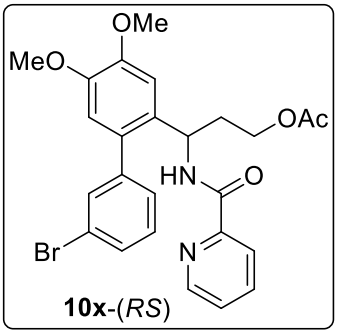
IR (DCM): 3375, 1736, 1513 cm^{-1};

^1H NMR (400 MHz, $CDCl_3$): δ_H 8.56 (1H, d, J = 3.0 Hz), 8.51 (1H, d, J = 7.0 Hz), 8.16 (1H, d, J = 7.7 Hz), 7.85 (1H, t, J = 7.6 Hz), 7.58 (1H, s), 7.52 (1H, d, J = 8.1 Hz), 7.45-7.43 (2H, m), 6.96 (1H, s), 6.68 (1H, s), 5.33-5.28 (1H, m), 4.04-3.99 (1H, m), 3.94-3.90 (1H, m), 3.90 (3H, s), 3.86 (3H, s), 2.17-2.09 (1H, m), 2.07-1.98 (1H, m), 1.92 (3H, s);

$^{13}C\{^1H\}$ NMR (~101 MHz, $CDCl_3$): δ_C 170.7, 163.6, 149.7, 149.3, 148.1, 148.0, 140.7, 137.4, 132.3, 131.6, 131.5, 131.3, 130.2, 129.4, 126.3, 122.2, 113.3, 109.1, 109.0, 61.2, 56.2, 56.0, 48.1, 35.6, 20.6;

HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{25}H_{25}Cl_2N_2O_5$: 503.1141; found: 503.1150.

3-(3'-Bromo-4,5-dimethoxy-[1,1'-biphenyl]-2-yl)-3-(picolinamido)propyl acetate (10x-(RS)): The compound **10x**-(RS) was obtained from procedure G after purification by column chromatography on silica gel (EtOAc:hexanes = 50:50) as a brown colour semi-solid (38 mg, 74%, 0.1 mmol scale);



R_f (EtOAc/hexanes = 50:50) 0.4;

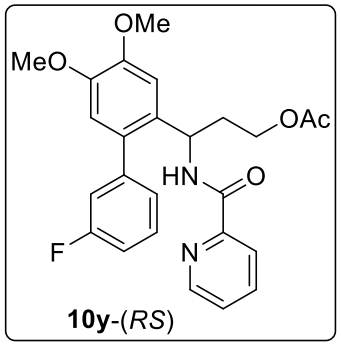
IR (DCM): 3221, 1703, 1373 cm^{-1};

^1H NMR (400 MHz, $CDCl_3$): δ_H 8.64 (1H, d, J = 7.5 Hz), 8.58-8.56 (1H, m), 8.20 (1H, d, J = 7.8 Hz), 7.89 (1H, td, J_1 = 7.7 Hz, J_2 = 1.6 Hz), 7.61 (1H, br. s), 7.53-7.46 (3H, m), 7.34 (1H, t, J = 7.8 Hz), 6.99 (1H, s), 6.69 (1H, s), 5.37-5.32 (1H, m), 4.04-3.98 (1H, m), 3.91 (3H, s), 3.90-3.87 (1H, m), 3.86 (3H, s), 2.17-2.10 (1H, m), 2.07-2.00 (1H, m), 1.92 (3H, s);

$^{13}C\{^1H\}$ NMR (~101 MHz, $CDCl_3$): δ_C 170.8, 163.1, 149.4, 149.0, 148.0, 147.6, 142.8, 138.0, 132.6, 132.5, 131.2, 130.2, 129.8, 128.6, 126.4, 122.7, 122.4, 113.3, 108.9, 61.3, 56.2, 56.0, 48.2, 35.4, 20.8;

HRMS (ESI): *m/z* $[M + Na]^+$ calcd for $C_{25}H_{25}BrN_2NaO_5$: 535.0845; found: 535.0824.

3-(3'-Fluoro-4,5-dimethoxy-[1,1'-biphenyl]-2-yl)-3-(picolinamido)propyl acetate (10y-(RS)): The compound **10y**-(RS) was obtained from procedure G after purification by column chromatography on silica gel (EtOAc:hexanes = 50:50) as a brown semi-solid (23 mg, 51%, 0.1 mmol scale);



10y-(*RS*)

R_f (EtOAc/hexanes = 50:50) 0.5;

IR (DCM): 3367, 1736, 1515 cm^{-1};

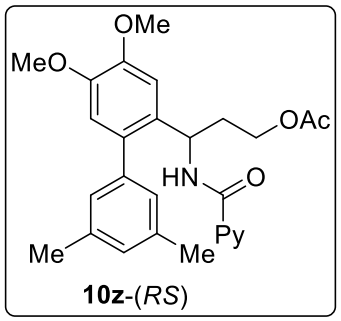
^1H NMR (400 MHz, $CDCl_3$): δ_H 8.59-8.55 (2H, m), 8.17 (1H, d, J = 7.8 Hz), 7.86 (1H, td, J_1 = 7.7 Hz, J_2 = 1.6 Hz), 7.47-7.39 (2H, m), 7.31 (1H, d, J = 7.6 Hz), 7.22 (1H, d, J = 9.6 Hz), 7.09- 7.04 (1H, m), 6.97 (1H, s), 6.72 (1H, s), 5.40-5.34 (1H, m), 4.02-3.97 (1H, m), 3.94-3.87 (1H, m), 3.91 (3H, s), 3.86 (3H, s), 2.16-2.00 (2H, m), 1.92 (3H, s);

$^{13}C\{^1H\}$ NMR (~101 MHz, $CDCl_3$): δ_C 170.9, 163.2, 162.6 (d, J_{C-F} = 245.1 Hz), 149.5, 149.0, 147.9, 147.7, 142.8 (d, J_{C-F} = 7.8 Hz), 137.9, 132.8, 131.2, 129.8 (d, J_{C-F} = 8.5 Hz), 126.4, 125.6 (d, J_{C-F} = 2.5 Hz), 122.5, 116.8 (d, J_{C-F} = 21.1 Hz), 114.0 (d, J_{C-F} = 20.9 Hz), 113.2, 108.8, 61.3, 56.2, 56.0, 48.2, 35.4, 20.7;

$^{19}F\{^1H\}$ NMR (~376 MHz, $CDCl_3$): δ_F = -112.94.

HRMS (ESI): *m/z* $[M + Na]^+$ calcd for $C_{25}H_{25}FN_2NaO_5$: 475.1645; found: 475.1652.

3-(4,5-Dimethoxy-3',5'-dimethyl-[1,1'-biphenyl]-2-yl)-3-(picolinamido)propyl acetate (10z-(RS)): The compound **10z**-(RS) was obtained from procedure G after purification by column chromatography on silica gel (EtOAc:hexanes = 50:50) as a brown colour semi-solid (41 mg, 59%, 0.15 mmol scale);



10z-(*RS*)

R_f (EtOAc/hexanes = 50:50) 0.5;

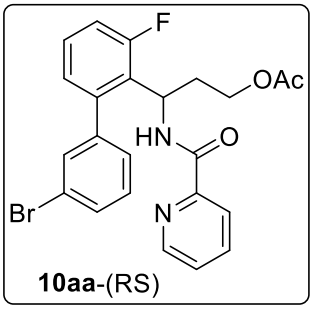
IR (DCM): 3379, 1735, 1511 cm^{-1};

^1H NMR (400 MHz, $CDCl_3$): δ_H 8.58-8.55 (2H, m), 8.20 (1H, d, J = 7.8 Hz), 7.87 (1H, td, J_1 = 7.8 Hz, J_2 = 1.3 Hz), 7.47-7.44 (1H, m), 7.05 (2H, br. s), 7.00 (2H, s), 6.72 (1H, s), 5.42-5.36 (1H, m), 3.99-3.88 (2H, m), 3.92 (3H, s), 3.85 (3H, s), 2.36 (6H, s), 2.17-2.02 (2H, m), 1.90 (3H, s);

$^{13}C\{^1H\}$ NMR (~101 MHz, $CDCl_3$): δ_C 170.8, 163.0, 149.7, 148.4, 147.8, 147.6, 140.6, 137.8, 137.8, 134.5, 130.8, 128.7, 127.4, 126.3, 122.5, 113.6, 109.2, 61.6, 56.2, 55.9, 48.6, 35.2, 21.4, 20.7;

HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{27}H_{31}N_2O_5$: 463.2233; found: 463.2241.

3-(3'-Bromo-3-fluoro-[1,1'-biphenyl]-2-yl)-3-(picolinamido)propyl acetate (10aa-(RS)):



10aa-(RS)

The compound **10aa**-(RS) was obtained from procedure G after purification by column chromatography on silica gel (EtOAc:hexanes = 50:50) as a brown colour semi-solid (57 mg, 60%, 0.20 mmol scale);

R_f (EtOAc/hexanes = 50:50) 0.65;

IR (DCM): 3396, 1738, 1515 cm^{-1};

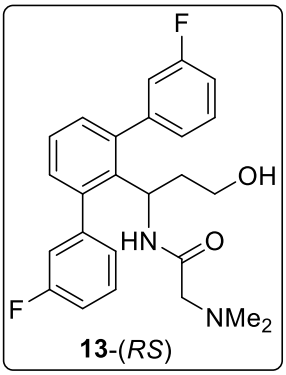
^1H NMR (400 MHz, $CDCl_3$): δ_H 8.78 (1H, d, J = 9.4 Hz), 8.56 (1H, d, J = 4.6 Hz), 8.16 (1H, d, J = 7.8 Hz), 7.81 (1H, td, J_1 = 7.7 Hz, J_2 = 1.5 Hz), 7.56-7.54 (3H, m), 7.42-7.36 (2H, m), 7.30-7.25 (1H, m), 7.13-7.08 (1H, m), 7.01 (1H, d, J = 7.6 Hz), 5.60-5.54 (1H, m), 4.04-3.98 (1H, m), 3.91-3.85 (1H, m), 2.33-2.25 (1H, m), 2.22-2.14 (1H, m), 1.84 (3H, s);

$^{13}C\{^1H\}$ NMR (~101 MHz, $CDCl_3$): δ_C 170.8, 163.3, 162.0 (d, J_{C-F} = 244.0 Hz), 149.6, 148.1, 142.0 (d, J_{C-F} = 5.0 Hz), 141.6 (d, J_{C-F} = 2.5 Hz), 137.2, 132.3, 130.6, 129.7, 128.6 (d, J_{C-F} = 9.7 Hz), 128.3, 126.3 (d, J_{C-F} = 12.0 Hz), 126.2, 126.1, 122.3, 122.2, 115.7 (d, J_{C-F} = 22.6 Hz), 61.0, 45.4, 34.2, 20.6;

$^{19}F\{^1H\}$ NMR (~376 MHz, $CDCl_3$): δ_F = -115.40.

HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{23}H_{21}BrFN_2O_3$: 471.0720; found: 471.0716.

***N*-(1-(3,3''-Difluoro-[1,1':3',1''-terphenyl]-2'-yl)-3-hydroxypropyl)-2-(dimethylamino)acetamide (13-(RS)):** The compound **13**-(RS) was obtained from procedures H, I and J after purification by column chromatography on silica gel (EtOAc:hexanes = 100:00) as a colourless semi-solid (48 mg, 52%, 0.218 mmol scale);



13-(*RS*)

R_f (EtOAc:hexanes = 100:00) 0.2;

IR (DCM): 3345, 1661, 1513 cm^{-1};

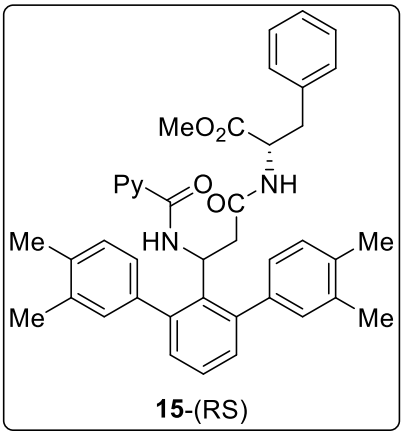
^1H NMR (400 MHz, $CDCl_3$): δ_H 7.44-7.37 (3H, m), 7.32 (1H, t, J = 7.6 Hz), 7.20-7.13 (5H, m), 7.11-7.08 (3H, m), 5.50-5.44 (1H, m), 3.35-3.30 (1H, m), 3.18-3.12 (1H, m), 2.87 (1H, d, J = 16.4 Hz), 2.71 (1H, d, J = 16.4 Hz), 2.12 (6H, s), 1.87-1.79 (1H, m), 1.69-1.61 (1H, m) (one signal perhaps corresponding to OH is not precisely located);

$^{13}C\{^1H\}$ NMR (~101 MHz, $CDCl_3$): δ_C 170.8, 162.4 (d, J_{C-F} = 246.2 Hz), 143.6 (d, J_{C-F} = 7.4 Hz), 141.1, 136.6, 130.9, 129.7 (d, J_{C-F} = 8.3 Hz), 126.5, 125.5, 116.7 (d, J_{C-F} = 21.2 Hz), 114.5 (d, J_{C-F} = 20.6 Hz), 62.6, 58.7, 46.7, 45.7, 40.5;

$^{19}F\{^1H\}$ NMR (~376 MHz, $CDCl_3$): δ_F = -112.28.

HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{25}H_{27}F_2N_2O_2$: 425.2041; found: 425.2034.

Methyl (3-(picolinamido)-3-(3,3'',4,4''-tetramethyl-[1,1':3',1''-terphenyl]-2'-yl)propanoyl)-*L*-phenylalaninate (15-(RS)): The compound **15**-(RS) was obtained from procedures K and L after purification by column chromatography on silica gel (EtOAc:hexanes = 30:70) as a colourless semi-solid (mixture of diastereomers, 38 mg, 59%, 0.10 mmol scale);



15-(RS)

R_f (EtOAc/hexanes = 30:70) 0.4;

IR (DCM): 3379, 1675, 1509 cm^{-1};

^1H NMR (400 MHz, $CDCl_3$): δ_H 8.45 (1H, d, J = 4.4 Hz), 8.41 (1H, d, J = 4.4 Hz), 8.21 (1H, d, J = 8.8 Hz), 8.09-8.02 (3H, m), 7.81-7.76 (2H, m), 7.40-7.36 (3H, m), 7.31-7.28 (3H, m), 7.23-7.17 (17H, m), 7.14-7.04 (4H, m), 6.99-6.96 (2H, m), 6.91-6.89 (2H, m), 6.26 (1H, d, J = 7.3 Hz), 5.97-5.91 (1H, m), 5.88-5.82 (1H, m), 4.66-4.58 (2H, m), 3.60 (3H, s), 3.46 (3H, s), 2.92-2.81 (3H, m), 2.78-2.67 (5H, m), 2.32 (9H, s), 2.32 (6H, s), 2.25 (9H, br. s);

$^{13}C\{^1H\}$ NMR (~101 MHz, $CDCl_3$): δ_C 171.6, 171.5, 169.4, 169.2, 163.3, 163.1, 149.6, 149.6, 147.8, 147.5, 142.1, 142.0, 139.4, 139.4, 137.0, 136.9, 136.7, 136.6, 136.2, 136.2, 136.1,136.0, 135.6, 135.6, 130.8, 130.7, 130.6, 129.6, 129.6, 129.1, 129.0, 128.4, 128.4, 126.9, 126.8, 126.7, 126.7, 126.4, 126.4, 125.9, 125.8, 122.1, 121.9, 53.3, 52.0, 51.9, 48.9, 48.3, 44.5, 38.0, 37.8, 19.8, 19.6 (the proton and carbon NMR values corresponds to diastereomers);

HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{41}H_{42}N_3O_4$: 640.3175; found: 640.3196.

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Chapter 6

Palladium(II)-Catalyzed sp^3/sp^2 γ- and δ-C-H Functionalization of Aryl Amines Using 5-Methylisoxazole-3-Carboxamide as Directing Group: En Route to 5-Methylisoxazole-3-Carboxamide Motifs.

For the purpose of this thesis work, the work of chapter 6 is re-used (adapted) with the permission from the publication, Singh, P.; Dalal, A.; Babu, S. A*. *Asian J. Org. Chem*. **2019**, *8*, 877-886. Title: Palladium(II)-Catalyzed $sp^3/sp^2\gamma$- and δ-C-H Functionalization of Aryl Amines using 5-Methylisoxazole-3-Carboxamide as Directing Group: en route to 5-methylisoxazole-3-carboxamide motifs.

The transition metal-catalyzed C-H activation/functionalization is an imperious synthetic transformation.[1-3] Especially, substantial advancements have been achieved on the Pd(II)-catalyzed site-selective C-H functionalization of carboxamides with the help of bidentate- or monodentate directing groups (DGs).[3] The Pd(II)-catalyzed site-selective C–H functionalization of carboxylic acids (substrate type I, Figure 1) have been accomplished using 8-aminoquinoline as the DG (Figure 1).[2-5]

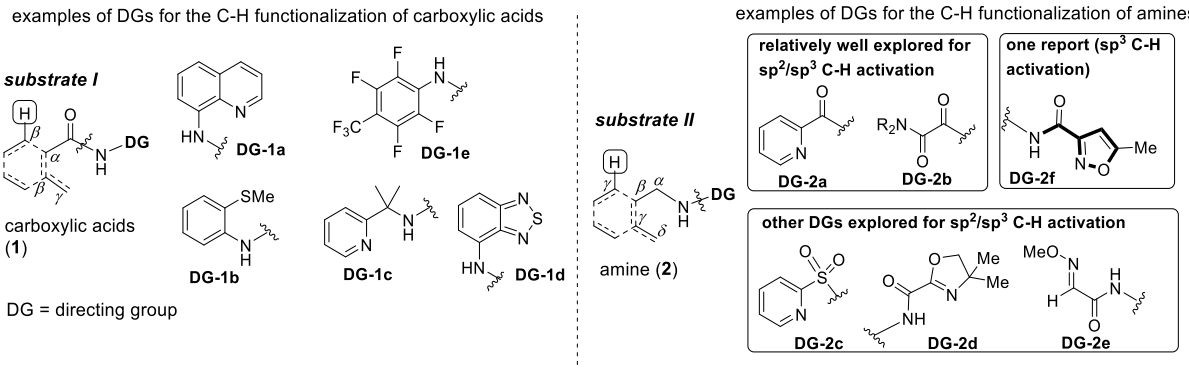


Figure 1. C-H Functionalization-aided by DGs

On the other hand, the Pd(II)-catalyzed site-selective C-H functionalization of amines (substrate type II, Figure 1) have been accomplished using picolinamide moiety (**DG-2a**) as the DG.[2,3,6-8] As a part of advancement on the use of various DGs for the C-H activation/functionalization amine/amino acid derivatives, other DGs similar to picolinamide such as, oxalyl amide moiety (**DG-2b**),[7d] *N*-(2-pyridyl)sulfonyl moiety (**DG-2c**),[7c] oxazoline moiety (**DG-2d**),[7f] 2-methoxyiminoacetyl moiety (**DG-2e**)[7e] and 5-methylisoxazole-3-carboxamide (MICA) moiety (**DG-2f**)[7a] have also been introduced. While these DGs were efficient, some of the DGs are not commercially available (e.g., **DG-2b**, **DG-2c**, **DG-2d** and **DG-2e**). Since their introduction, the **DG-2a** and to some extent the **DG-2b** have been

relatively well explored. On the other hand, the **DG-2c**, **DG-2d** and **DG-2e** and **DG-2f** (MICA) have been relatively less exposed and their use for the C-H functionalization of different amine derivatives has yet to be expanded.

Isoxazole carboxamide-based small molecules are noteworthy in medicinal chemistry and drug discovery.[9,10] Notably, MICA moiety-based small molecules have been found to exhibit different biological activities and used as medicines (Figure 2).[10] E.g., Leflunomide and leflunomide analogs (**3a**) are immunosuppressive disease-modifying antirheumatic drug (DMARD) molecules.[10a,b] The MICA derivatives **3b** and **3c** have been evaluated as irreversible human rhinovirus 3C protease inhibitors[10c] and DFG-out p38α inhibitor, respectively.[10d] The MICA derivative **3d** was shown as an SMN2-luciferase reporter.[10e]

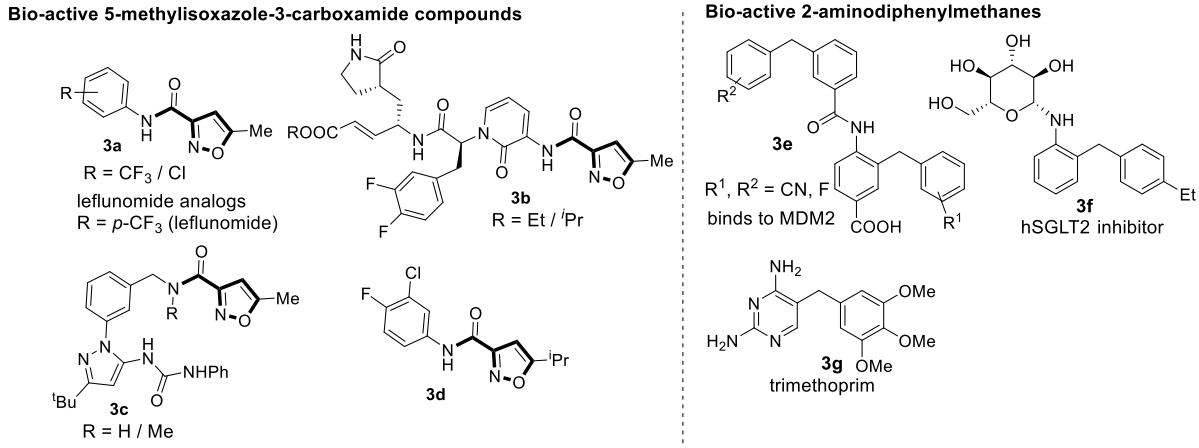
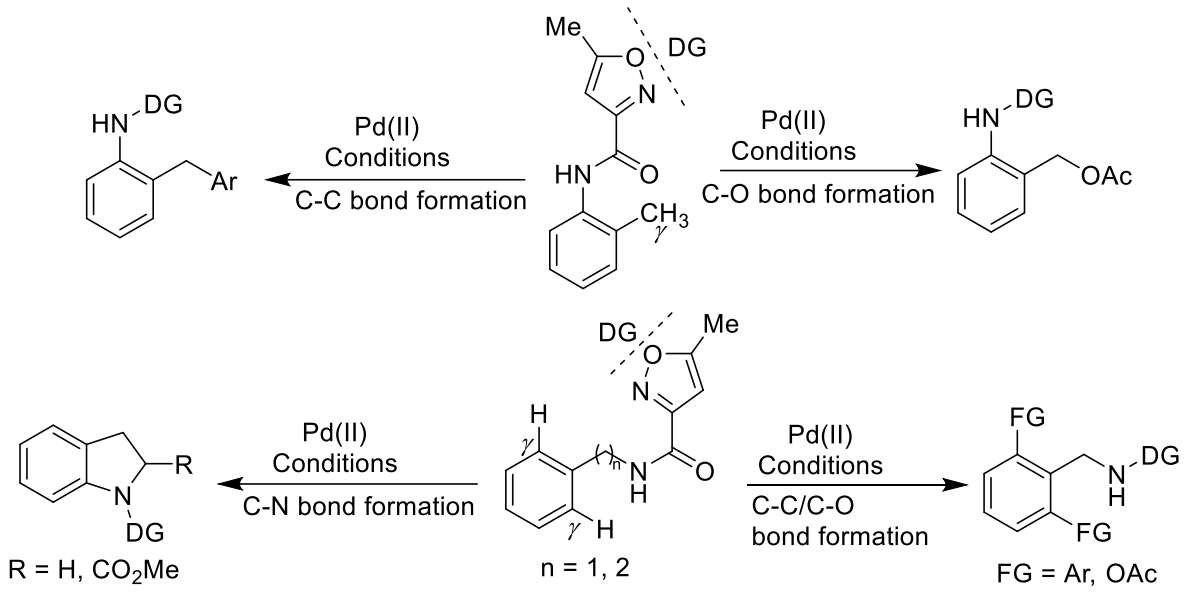


Figure 2. Examples of bio-active MICA-based motifs and 2-aminodiphenylmethanes

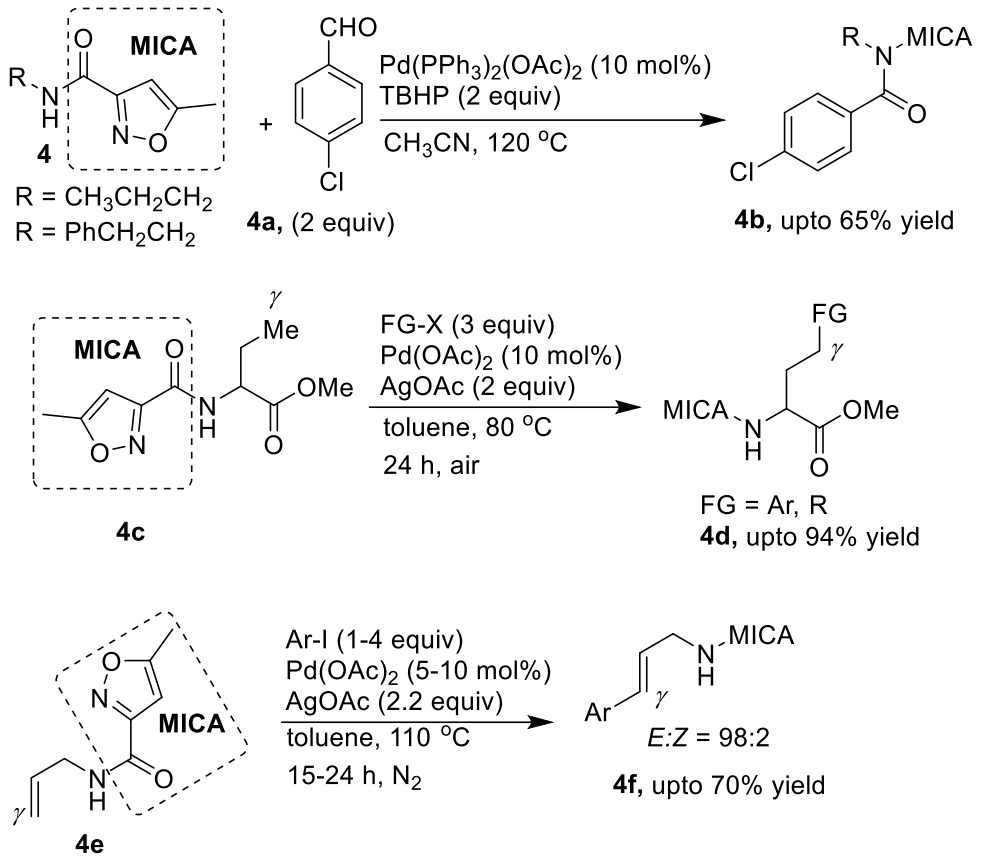
Considering the importance of MICA-based derivatives in medicinal chemistry and drug discovery, assembling of new libraries of MICA motifs would be appreciated. Along this line and in continuation of our lab's research program on the DG-aided C-H activation reactions, we envisioned to expand the usage of MICA as the DG for the sp^3/sp^2 C-H functionalization of different aryl amines and assemble libraries of MICA motifs. Accordingly, we report a dual objective-based study comprising the exploration of the Pd(II)-catalyzed sp^3/sp^2 γ- and δ-C-H functionalization reactions using MICA as a DG and assembling of new libraries of MICA-based motifs (Scheme 1).



Scheme 1. Exploration of MICA as the DG

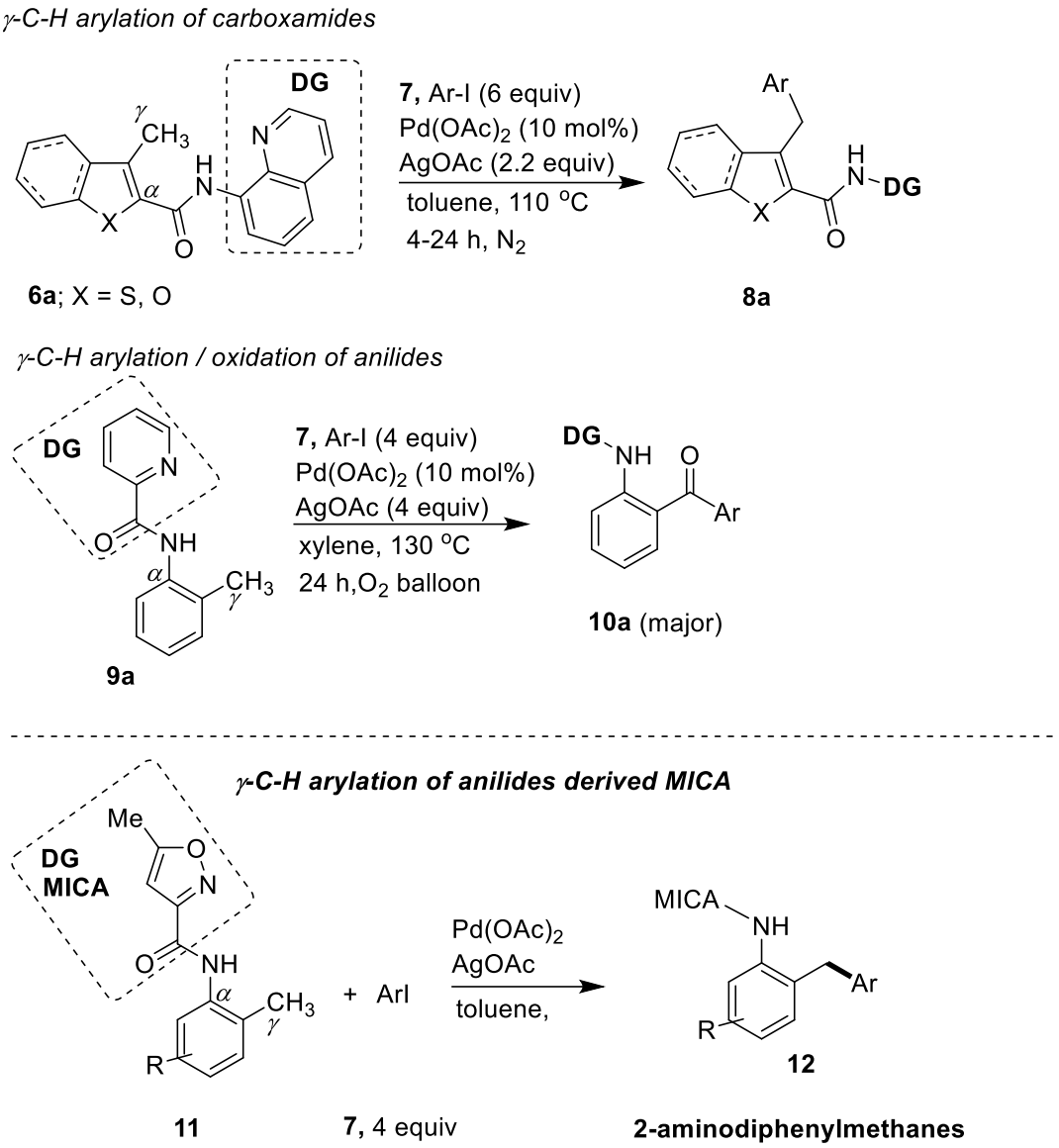
Literature reports dealing with 5-Methylisoxazole-3-Carboxamide (MICA) as a directing group:

Huang's group in 2013[7b] employed the MICA moiety to synthesize imides using the palladium (II)-catalyzed C-H functionalization of aldehydes with various *N*-substituted *N*-heteroarene-2-carobxmides.The reaction condition uses substrate **4** (1 equiv), $Pd(Ph_3P)_2(OAc)_2$ (10 mol%), TBHP (2 equiv), aromatic aldehyde **4a** (2 equiv) in acetonitrile at 120 ^oC for 24 h to get the *N*-substituted *N*-heteroarene-2-carobxmides **4b**. The reaction protocol is applicable to variety of functionalities and reaction is believed to follow Pd^{II}/Pd^{IV} pathway. In the continuation Liu *et al.* in 2015[7a] utilizes MICA as a directing group for C-H arylation of γ-C(sp^3)-H bonds. Under the reaction condition selective arylation and alkylation of various α-aminobutanoic acids was performed which led to construction of unnatural amino acids. They have also shown the synthesis of (-)-Banalol *via* functional group conversion after C-H alkylation of α-aminobutanoic acids. The optimal reaction condition involves substrate **4c** (1 equiv), $Pd(OAc)_2$ (10 mol%), AgOAc (2 equiv), FG-X (3 equiv) in toluene at 80 ^oC for 24 h under air to furnish the corresponding C-H functionalized product **4d**. Our group have also used MICA as a directing group[8] for Pd(II)-catalyzed, γ-C(sp^2)-H arylation of allylamine derivative. We have obtained E-selective γ-C(sp^2)-H arylated product **4f** under the reaction condition which was in contrast to Picolinamide as a DG which produces Z-selective C(sp^2)-H arylation. So it was proposed that reaction was happening *via* typical Heck-type mechanism rather chelation assisted C-H arylation pathway (Scheme 2a).



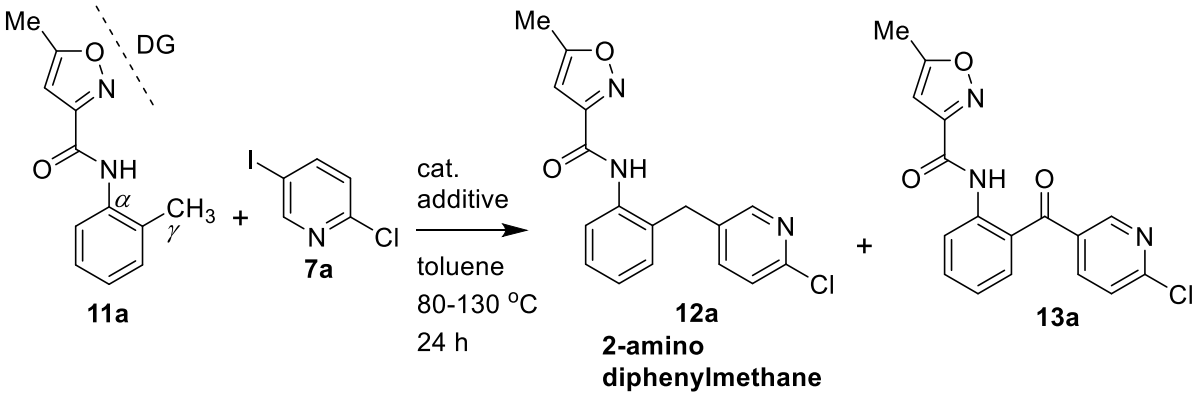
Scheme 2a. Representative literature reports of MICA as a directing group

Zhao's wand co-workers in 2012[6a] reported Pd(II)-catalyzed picolinamide assisted *γ*-C-H arylation of *o*-toluidine moiety, leading to the synthesis of various diaryl ketones with good to excellent yields. The optimal reaction condition consists of substrate **9a** (1 equiv), $Pd(OAc)_2$ (10 mol%), AgOAc (4 equiv), Ar-I (4 equiv) in xylene at 130 °C for 24 h to afford **10a**. Our group has also described the Pd(II)-catalyzed 8-aminoquinoline-aided *γ*-C-H arylation of benzylic methyls of carboxylic acid derivatives **6a** (Scheme 2b).[4b] Taking an impetus from these works, we envisaged attempting the Pd(II)-catalyzed *γ*-C(sp^3)-H arylation of benzylic methyls of *ortho*-toluidines **11** (Scheme 2b). This reaction would afford 2-aminodiphenylmethane (unsymmetrical diarylmethane) motifs **12**. It is to be noted that 2-aminodiphenylmethane motifs are prevalent in medicinal chemistry, and representative examples of bio-active 2-aminodiphenylmethanes are shown in Figure 2.[11]



Scheme 2b. sp^3/sp^2 γ-C-H Functionalization.

Table 1. Optimization reactions. Construction of **12a** via the Pd(II)-catalyzed, MICA-aided γ-C(sp^3)-H arylation of **11a**[a]



Entry	Catalyst [10 mol%]	Metal salt [0.44 mmol]	Additive [0.04 mmol]	T [°C]	12a: yield [%]
1	$Pd(OAc)_2$	KOAc	-	110	32
2	$Pd(OAc)_2$	Ag_2CO_3	-	110	40
3	**$Pd(OAc)_2$**	**AgOAc**	**-**	**110**	**50**
4[b]	**$Pd(OAc)_2$**	**AgOAc**	**-**	**130**	**49**
5	$Pd(OAc)_2$	AgOAc	$(BnO)_2PO_2H$	110	47
6	$Pd(OAc)_2$	AgOAc	PivOH	110	42
7	$Pd(OAc)_2$	AgOAc	Ph_3P	110	38
8	$Pd(OAc)_2$ [20 mol%]	AgOAc	Ph_3P	110	45
9	$Pd(OAc)_2$	AgOAc	PivOH	110	42
10	$Pd(OAc)_2$	AgOAc	TfOH	110	-
11	$Pd(OAc)_2$	K_2CO_3	PivOH	110	-
12[c]	$Pd(OAc)_2$	K_2CO_3	-	80	-
13	$PdCl_2$	AgOAc	-	110	38
14	$Pd(PPh_3)_2Cl_2$	AgOAc	-	110	34
15	$Pd(MeCN)_2Cl_2$	AgOAc	-	110	36
16	$Pd(TFA)_2$	AgOAc	-	110	46
17	$Pd(dba)_2$	AgOAc	-	110	30
18	$Ni(OTf)_2$	Na_2CO_3	-	130	-
19	$Pd(OAc)_2$ [20mol%]	AgOAc	-	110	45
20[d]	$Pd(OAc)_2$	AgOAc	-	100	33
21[e]	$Pd(OAc)_2$	AgOAc	-	80	38
22[f]	$Pd(OAc)_2$	AgOAc	-	110	30

[a] **11a** [0.2 mmol], **7a** [0.6 mmol] in toluene [2 mL] under a nitrogen atm. [b] Initially, the reaction was started using **7a** [0.6 mmol] and after 12 h another portion of **7a** [0.6 mmol] was

added. [c] Solvent = ^{t}BuOH. [d] Solvent = 1,4-dioxane. [e] Solvent = 1,2-DCE. [f] Along with the product **12a**, the compound **13a** was observed [5-8%]. Other corresponding reactions of Table 1 did not give the oxidation product **13a** in characterizable amounts.

Result and discussion:

To commence our study, initially we assembled the MICA-based substrate **11a** from *ortho*-toluidine and 5-methylisoxazole-3-carboxylic acid. Then, we attempted the construction of 2-aminodiphenylmethane **12a** via the Pd(II)-catalyzed, MICA-aided γ-C(sp^3)-H arylation of **11a**. In order to find out the suitable reaction conditions, which would give the product **12a** in good yield, we performed the optimization reactions comprising various Pd catalysts, metal salts/additives and solvents (Table 1).

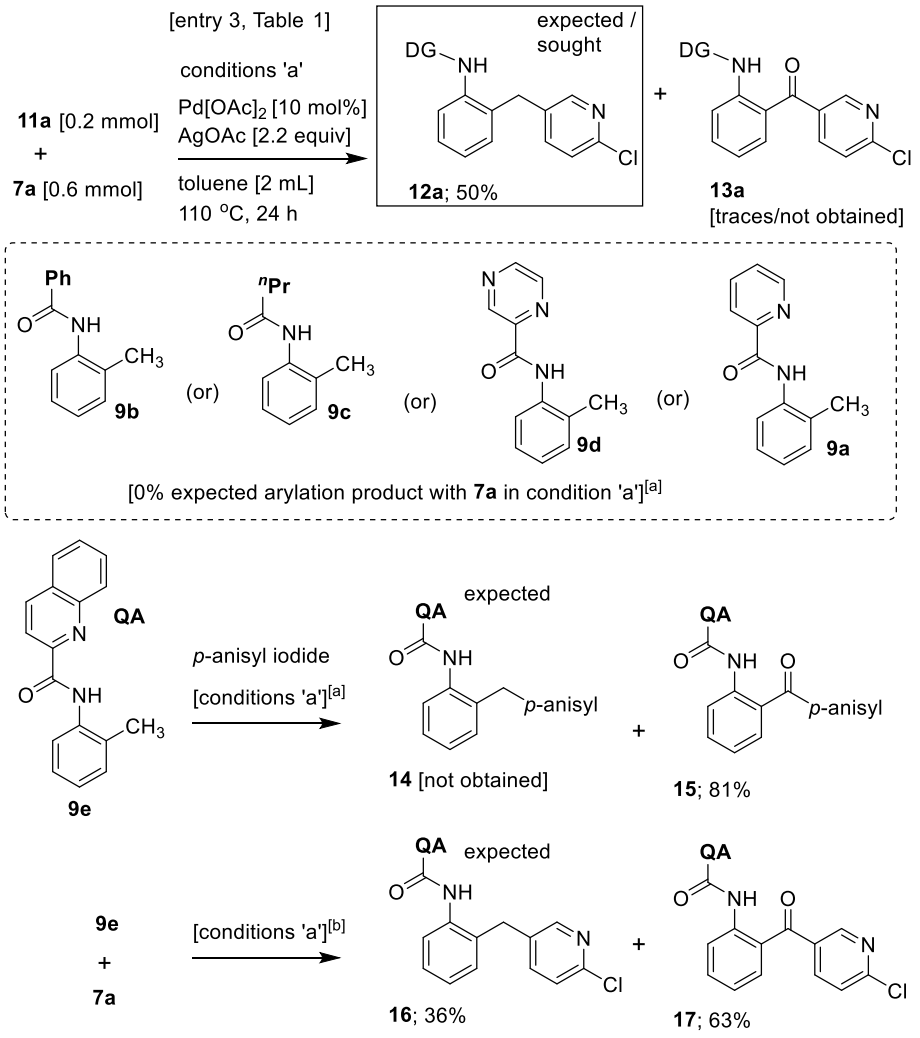
At the outset, we performed the reaction of a mixture of **11a**, heteroaryl iodide **7a**, $Pd(OAc)_2$ (10 mol%) and KOAc or Ag_2CO_3 or AgOAc (additive) in toluene at 110 ^{o}C for 24 h. These reactions afforded the expected 2-aminodiphenylmethane derivative **12a** in 32-50% yields via the MICA-aided arylation of benzylic methyl of **11a** (entries 1-3, Table 1). In an attempt to improve the yield of **12a**, an additional portion of **7a** was added to the reaction mixture after 12 h period and this reaction also afforded the product **12a** in only satisfactory yield (49%, entry 4, Table 1). It is well-known that the metal salt additive, e.g., AgOAc, Ag_2CO_3, KOAc, acts as an iodide ion (I^{-}) scavenger and also indirectly help in the regeneration of the Pd(II) catalyst.[2-8] We also intended to screen the reaction of **11a** and **7a** with additional additives to improve yield of **12a**. Accordingly, we performed the reactions using $(BnO)_2PO_2H$ or PivOH or Ph_3P or TfOH as an additional additive. Except the reaction involving TfOH, the other reactions again afforded the product **12a** in only 42-47% yields (entries 5-10, Table 1).

Further, the arylation of **11a** in the presence of K_2CO_3 as an additive failed to give the product **12a** (entries 11 and 12, Table 1). The arylation of **11a** using the $Ni(OTf)_2$ catalyst was not fruitful and the arylation of **11a** involving other Pd catalysts afforded the product **12a** in only 34-46% yields (entries 13-18, Table 1). The arylation of **11a** using 20 mol% of the $Pd(OAc)_2$ catalyst also gave the product **12a** in only 45% yield (entry 19, Table 1). The arylation of **11a** in other solvents such as, 1,4-dioxane, 1,2-DCE (1,2-dichloroethane) and *p*-xylene afforded the product **12a** in 30-38% yields (entries 20-22, Table 1). Only in the reaction which was performed in *p*-xylene, we observed the formation of the oxidation product **13a** in negligible yield (<8% yield).

We also performed some control experiments to recognize the role and relative effectiveness of MICA as the DG. Accordingly, we opted to investigate the effectiveness of MICA by

comparing the Pd(II)-catalyzed γ-C(sp^3)-H arylation of benzylic methyl of *ortho*-toluidine derivatives (Scheme 3). In this regard, initially we assembled the benzamide **9b** and butyramide **9c** from *ortho*-toluidine and their corresponding carboxylic acids.

Then, we independently subjected the carboxamides **9b,c** to the standard arylation conditions. The carboxamides **9b,c** did not undergo the γ-C(sp^3)-H arylation and the corresponding arylation products were not obtained (Scheme 3). These reactions indicated that it is necessary to use the bidentate DG, such as MICA (**DG-2f**) for an effective γ-C(sp^3)-H activation/arylation of benzylic methyl of an *ortho*-toluidine derivative.



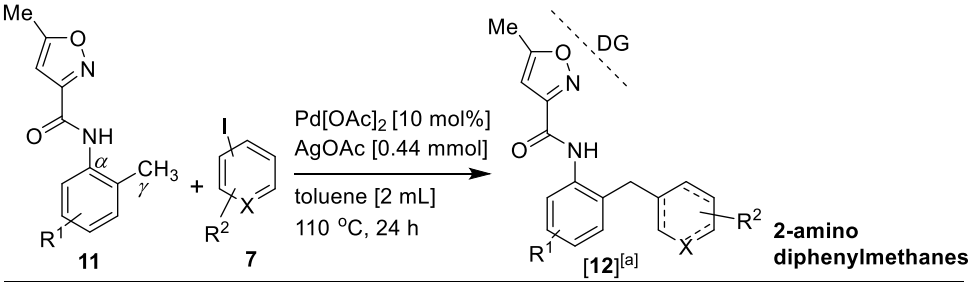
[a] Carboxamide (0.2-0.3 mmol) and ArI (0.6-0.9 mmol). [b] Carboxamide (0.2 mmol) and ArI (0.8 mmol).

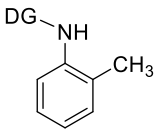
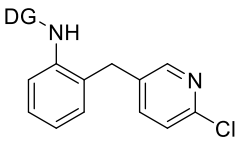
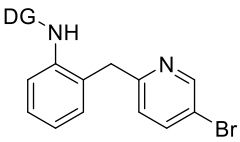
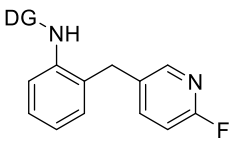
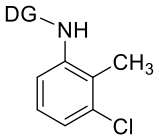
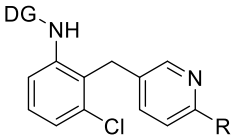
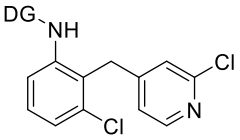
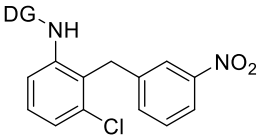
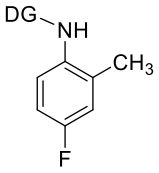
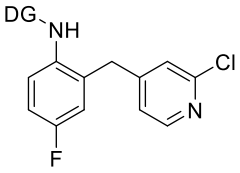
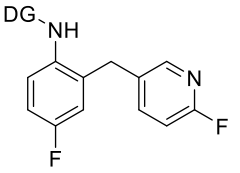
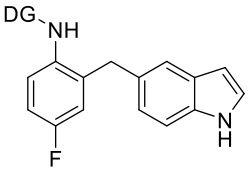
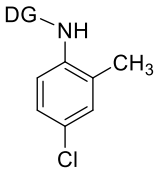
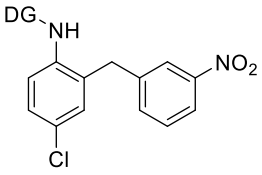
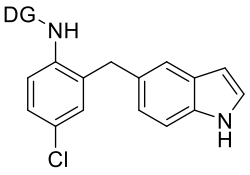
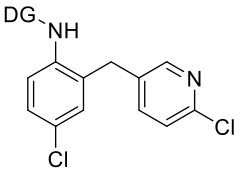
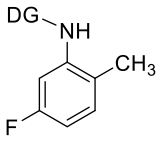
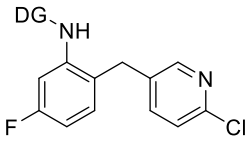
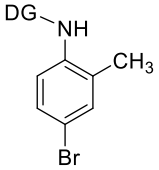
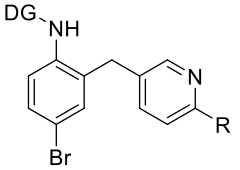
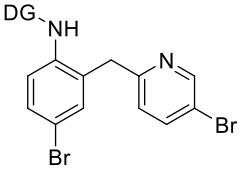
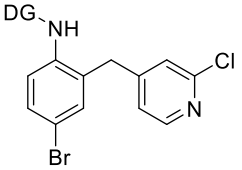
Scheme 3. Control experiments revealing the relative efficiency of MICA-aided γ-C(sp^3)-H arylation

It may be recalled that Zhang et al have described[6a] that the γ-C(sp^3)-H arylation of **9a** with *p*-tolyl iodide using the picolinamide **DG-2a** gave the ketone product **10a** as the major

compound (Scheme 2). Keeping this in mind, we also assembled the carboxamide **9e** (similar to **9a**) in which the quinoline-2-carboxamide moiety is expected to function as the DG similar to the picolinamide moiety in **9a** (Scheme 3). Not surprisingly, in accordance with the Zhang's work, the γ-C(sp^3)-H arylation of **9e** with *p*-anisyl iodide also afforded the ketone (arylation-oxidation) product **15** as the major compound (81%, Scheme 3).

However, the γ-C(sp^3)-H arylation of **9e** with **7a** afforded a mixture of both the γ-C–H arylation product **16** (36%) and the ketone (arylation-oxidation) product **17** (63%, Scheme 3). While we have not used any oxygen atm and performed the reactions under a nitrogen atm, the oxidized products **15** or **17** are presumably formed with the help of an adventitious oxygen atm under the experimental conditions. Additionally, it is to be noted that the γ-C(sp^3)-H arylation of pyrazine-2-carboxamide **9d** or **9a** with **7a** were also not fruitful (Scheme 3).



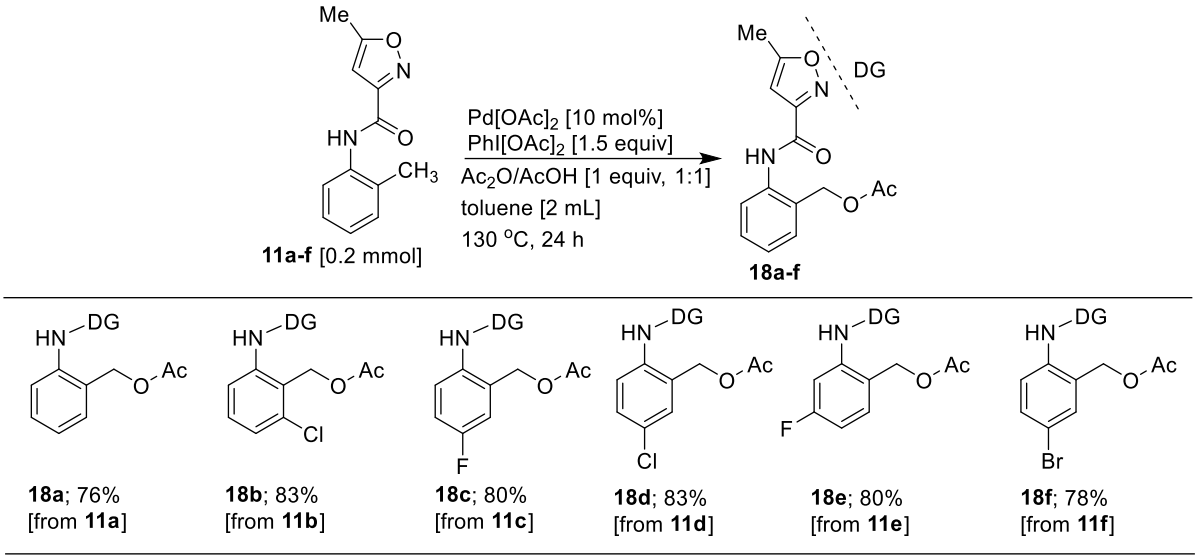
substrate [**11**]	product [**12a-r**]		
 **11a**	 **12a**; 50%	 **12b**; 42%	 **12c**; 35%
 **11b**	 **12d**; R= Cl, 45% **12f**; R= F, 42%	 **12e**; 40%	 **12g**; 35%
 **11c**	 **12h**; 45%	 **12i**; 42%	 **12j**; 35%
 **11d**	 **12k**; 50%	 **12l**; 35%	 **12m**; 35%
 **11e**	 **12n**; 35%		
 **11f**	 **12o**; R= Cl, 42% **12p**; R= F, 42%	 **12q**; 37%	 **12r**; 44%

Scheme 4. Pd(II)-catalyzed, MICA-aided γ-C(sp^3)-H arylation of *ortho*-toluidine derivatives **11**. Construction of 2-aminodiphenylmethanes **12**.

[a] Reactions were carried out using **11** [0.2 mmol], ArI **7** [0.6-1 mmol] under a nitrogen atm. All the reactions gave the products **12** and the corresponding ketone [oxidation] products similar to **10a/13a** were not obtained in characterizable amounts in the above reactions. In some other attempts, we observed that the MICA-aided C-H arylation of **11a** with other simple ArI [other than used in this Scheme, e.g., *m*-CF_3-C_6H_4-I, *m*-COOEt-C_6H_4-I and *p*-COOMe-C_6H_4-I] afforded an inseparable mixture of arylation and arylation-oxidation [ketone] products.

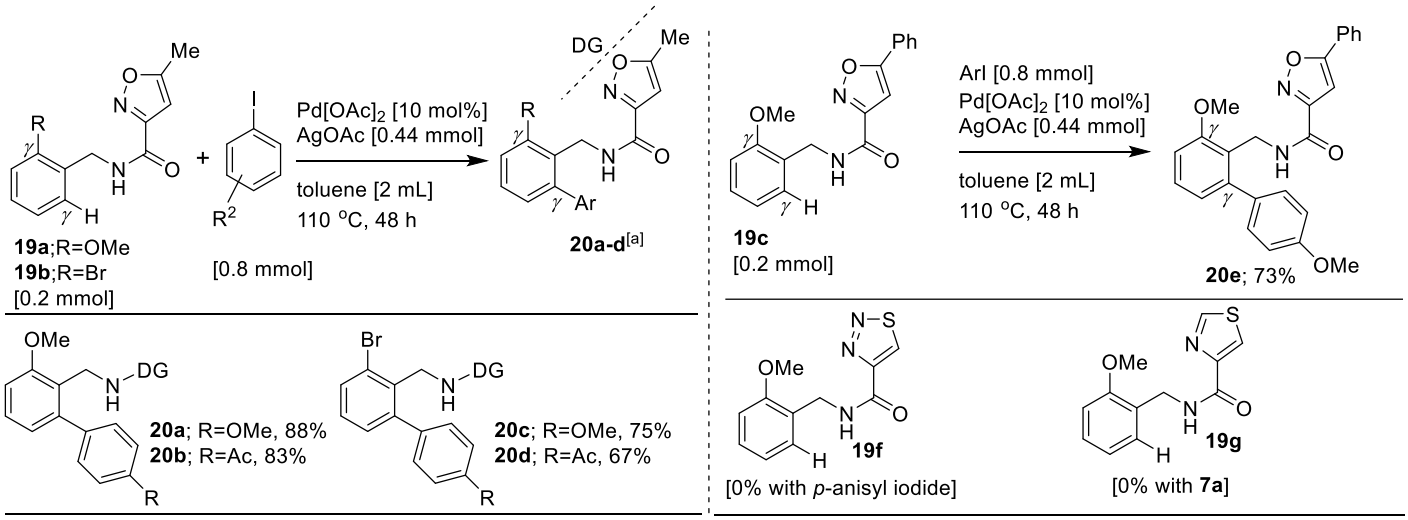
Having done the possible optimization and control reactions, we wished to investigate the scope of this MICA-aided γ-C(sp^3)-H arylation of benzylic methyls of *ortho*-toluidines. In this regard, we carried out the Pd(II)-catalyzed γ-C(sp^3)-H arylation of benzylic methyls of **11a** with different heteroaryl iodides, which afforded the corresponding 2-aminodiphenylmethane motifs **12a-c** in 35-50% yields (Scheme 4). Next, we assembled various MICA substrates **11b-f** from their corresponding *ortho*-toluidines containing different substituents (e.g., F, Cl and Br) in the aryl ring. After assembling the substrates **11b-f**, we then performed the Pd(II)-catalyzed γ-C(sp^3)-H arylation of **11b-f** with various heteroaryl iodides, which afforded the corresponding 2-aminodiphenylmethane motifs **12d-r** in 35-50% yields (Scheme 4).

It may be noted that our extensive attempts involving optimization reactions (Table 1) to improve the yield of product **12a** were not fruitful. The exact reasons for the selective formation of the γ-C(sp^3)-H arylated motifs **12** without the formation of ketone products in considerable amounts and the low yields obtained for the arylation products **12** are not known at this stage. However, these may be expounded based on the control experiments shown in Scheme 3. Earlier, Liu et al stated[1o] that in the transition metal-catalyzed, DG-aided C-H activation reactions, the strongly coordinating heteroatoms (e.g., N, S, etc) often out-compete the DGs for catalyst binding, thus this out-competence is presumably deterring the C-H activation process. Accordingly, the MICA-based substrates **11a-f** and various heteroaryl iodides **7** (e.g., iodopyridines) used for the γ-C(sp^3)-H arylation of **11a-f** altogether contain more than one coordinating nitrogen atoms/sites, which perhaps deterred the Pd(II)-based C-H activation and subsequent arylation processes. Based on the control reactions shown in Scheme 3, the MICA-aided C-H activation/arylation of **11** with heteroaryl iodides (**7**) are presumably sluggish when compared to the picolinamide- or quinoline-2-carboxamide-aided arylation reactions involving **9a,e** and simple aryl iodides (e.g., *p*-tolyl iodide or *p*-anisyl iodide). Thus, the MICA-aided C-H arylation of **11** with heteroaryl iodides have selectively afforded the γ-C(sp^3)-H arylation products **12** as the major compounds and in these cases, presumably the subsequent oxidation was not a facile reaction.



Scheme 5. Pd(II)-catalyzed, MICA-aided γ-C(sp^2)-H acetoxylation of *o*-toluidine derivatives **11a-f**.

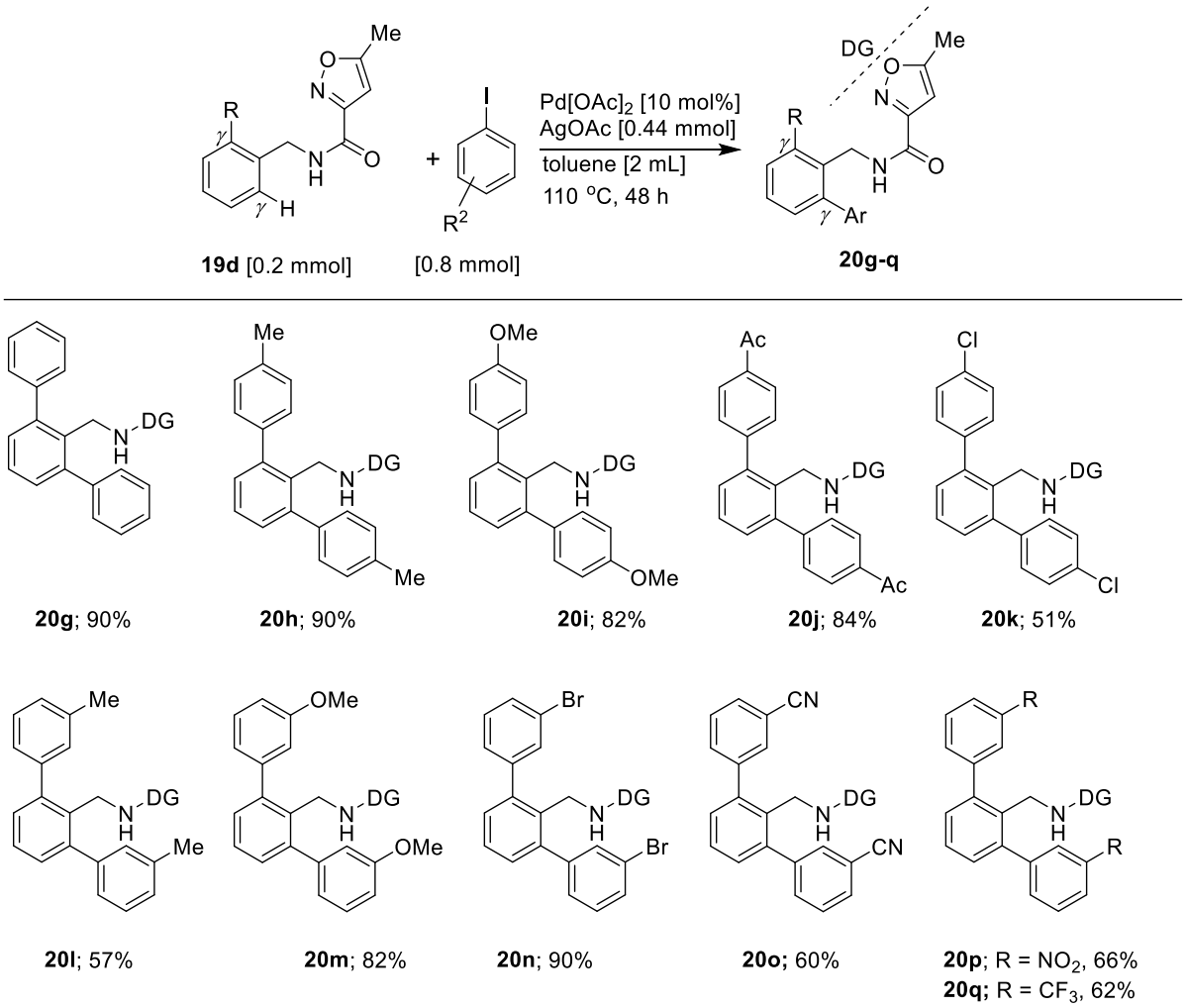
After investigating the MICA-aided γ-C(sp^3)-H arylation of **11**, we then intended to attempt the MICA-aided γ-C(sp^3)-H acetoxylation of benzylic methyls of *ortho*-toluidines **11** under the Pd(II)-catalyzed acetoxylation reaction conditions (Scheme 5).[2m,n,7g] Accordingly, the γ-C(sp^3)-H acetoxylation of **11a** with the acetoxylating reagent $PhI(OAc)_2$ in the presence of the $Pd(OAc)_2$ catalyst and Ac_2O/AcOH in toluene at 130 °C afforded the γ-C(sp^3)-H acetoxylated product **18a** (2-aminobenzyl acetate) in 76% yield. Having obtained the product **18a** in the previous attempt, we then performed the Pd(II)-catalyzed γ-C(sp^3)-H acetoxylation of benzylic methyls of the other *ortho*-toluidine derivatives **11b-f**, which afforded the corresponding γ-C(sp^3)-H acetoxylated products **18b-f** in 78-83% yields (Scheme 5).



Scheme 6. Pd(II)-catalyzed mono γ-C(sp^2)-H arylation of benzylamine derivatives **19a-c,f,g**.

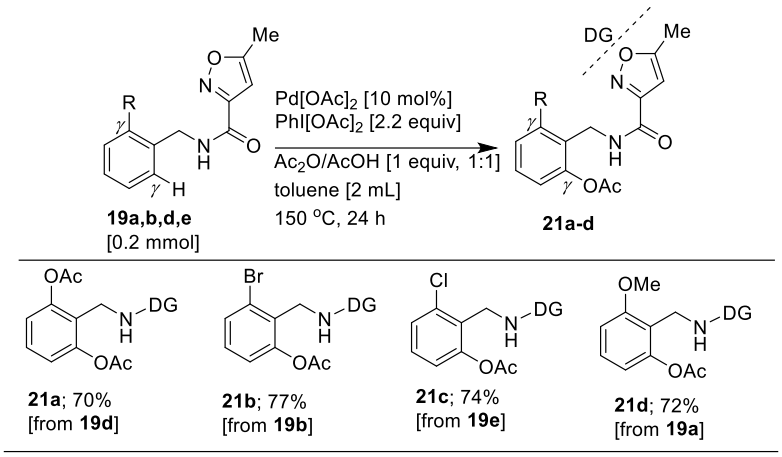
Next, to expand the scope of MICA-aided C-H functionalization, we intended to attempt the γ-C(sp^2)-H arylation of *ortho* C−H bonds of benzyl amines under the Pd(II)-catalyzed C-H arylation conditions (Scheme 6).[3e] Accordingly, the MICA-aided γ-C(sp^2)-H arylation of *ortho* C−H bond of benzylamine derivative **19a,b** with *p*-substituted aryl iodides in the presence of the $Pd(OAc)_2$ catalyst in toluene at 110 ^oC afforded the corresponding mono γ-C(sp^2)-H arylated products **20a-d** in 67-88% yields (Scheme 6). Similar to the MICA-based substrate **19a**, we also assembled the 5-phenylisoxazole-3-carboxamide (PICA) substrate **19c** from the corresponding benzyl amine and 5-phenylisoxazole-3-carboxylic acid. After assembling **19c**, we then performed the Pd(II)-catalyzed (PICA)-aided γ-C(sp^2)-H arylation of *ortho* C−H bond of **19c** with *p*-anisyl iodide in toluene at 110 ^oC. This reaction also afforded the mono γ-C(sp^2)-H arylated PICA-based product **20e** in 73% yield (Scheme 6). Furthermore, the Pd(II)-catalyzed γ-C(sp^2)-H arylation of *ortho* C−H bond of benzylamine derivatives **19f,g** were not fruitful as the corresponding 1,2,3-thiadiazole-4-carboxamide and thiazole-4-carboxamide moieties perhaps did not assist the *ortho* C-H arylation process as the DG in the substrates **19f,g** (Scheme 6).

To further expand the generality of the MICA-aided γ-C(sp^2)-H arylation reaction, we attempted the bis γ-C(sp^2)-H arylation of *ortho* C−H bonds of benzylamine derivative **19d**. The Pd(II)-catalyzed *ortho* C−H arylation of **19d** with PhI and different aryl iodides containing electron-donating or withdrawing groups (e.g., Me, OMe, Ac, Cl, CN, Br, NO_2 and CF_3) at the *para* or *meta* position afforded the various bis γ-C(sp^2)-H arylated products **20g-q** in 51-90% yields, respectively (Scheme 7).



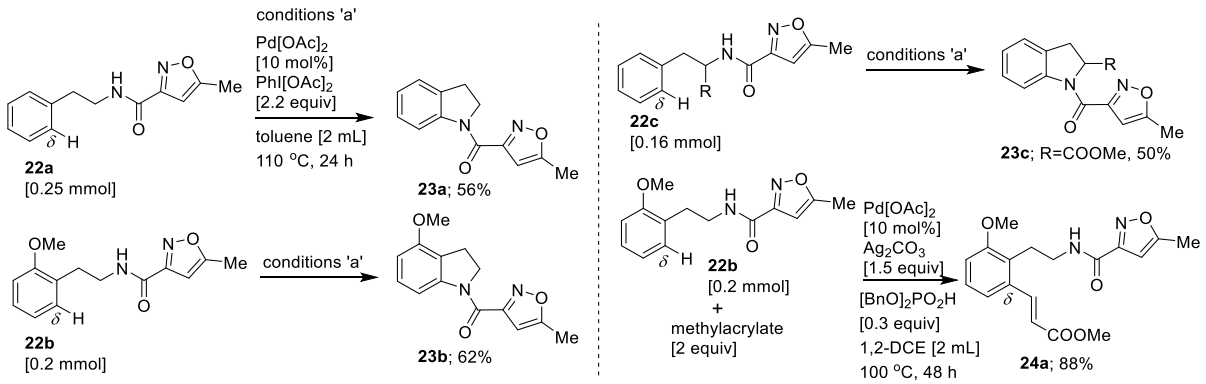
Scheme 7. Pd(II)-catalyzed, MICA-aided γ-C(sp^2)-H bis-arylation of benzylamine derivative **19d**.

Then, we wished to attempt the MICA-aided γ-C(sp^2)-H acetoxylation of benzyl amine derivatives **19a,b,d,e** under the Pd(II)-catalyzed acetoxylation reaction conditions (Scheme 8). Accordingly, the γ-C(sp^2)-H acetoxylation of benzyl amine derivative **19d** with the acetoxylating reagent $PhI(OAc)_2$ in the presence of the $Pd(OAc)_2$ catalyst and Ac_2O/AcOH in toluene at 150 °C afforded the bis γ-C(sp^2)-H acetoxylated product **21a** in 70% yield (Scheme 8). Successively, the Pd(II)-catalyzed MICA-aided mono γ-C(sp^2)-H acetoxylation of benzyl amine derivatives **19a,b,e** afforded the corresponding mono γ-C(sp^2)-H acetoxylated products **21b-d** in 72-77% yields (Scheme 8).

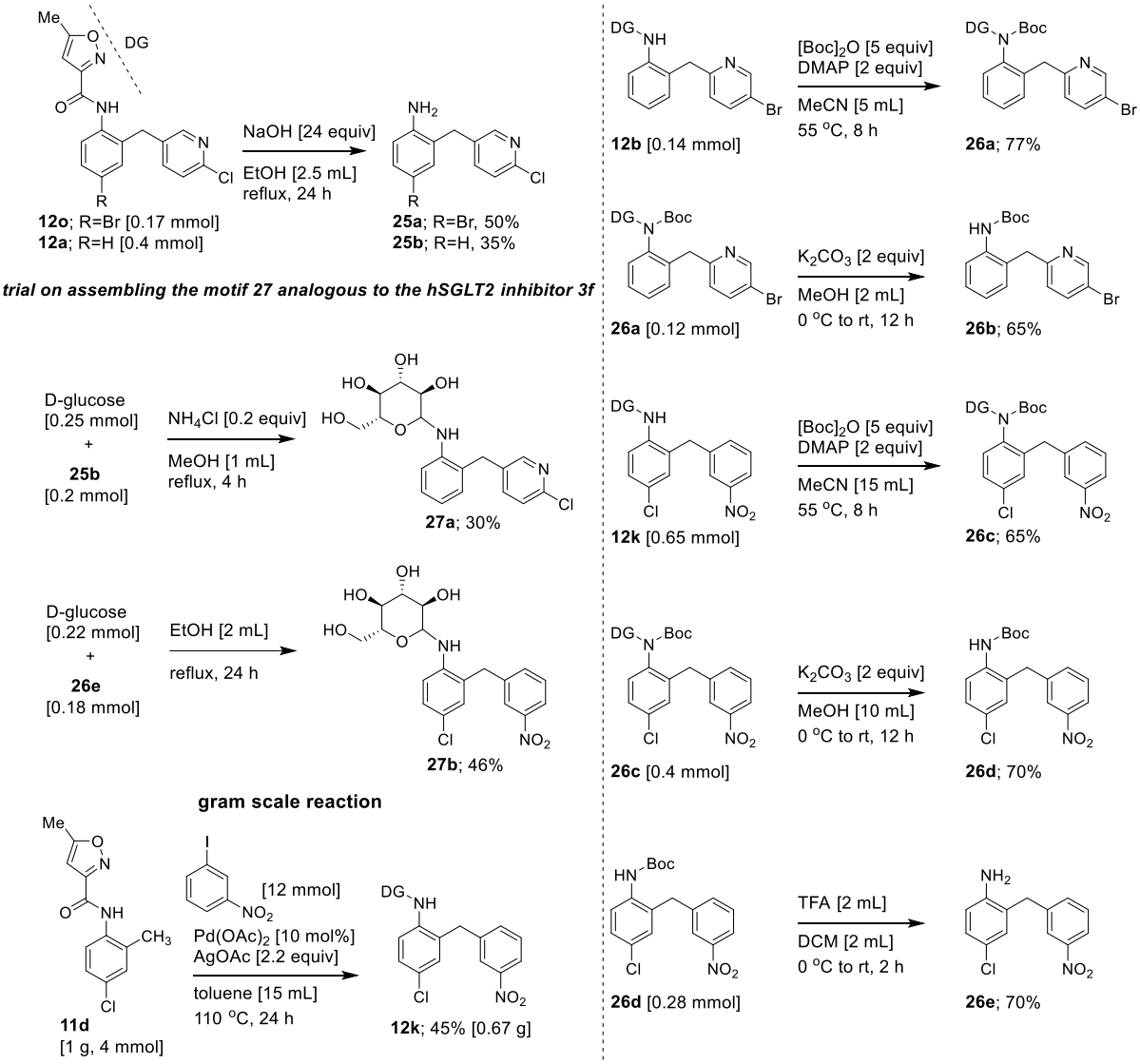


Scheme 8. Pd(II)-catalyzed, MICA-aided γ-C(sp^2)-H acetoxylation of benzylamine derivatives **19**.

To further explore the scope of the MICA-aided C-H activation reactions, we wished to attempt the intramolecular remote δ-C-H amidation/cyclization reactions (Scheme 9).[2,3c] In this regard, we assembled the MICA-based substrates **22a-c** from their corresponding phenethylamines and 5-methylisoxazole-3-carboxylic acid. After assembling the substrates **22a-c**, we attempted the MICA-aided remote δ-C(sp^2)-H amidation/cyclization of the substrate **22a** under the Pd(II)-catalyzed C-H amidation reaction conditions, which gave the indoline derivative **23a** in 56% yield (Scheme 9). Subsequently, the MICA-aided remote δ-C(sp^2)-H amidation/cyclization of substrates **22b,c** under the Pd(II)-catalyzed C-H amidation reaction conditions also gave the corresponding indoline derivatives **23b,c** in 50-62% yields (Scheme 9). To further reveal the utility of the MICA-aided C-H functionalization reaction, we attempted the remote δ-C(sp^2)-H alkenylation of the MICA-based substrate **22b** with methylacrylate under the Pd(II)-catalyzed C-H alkenylation reaction conditions,[6m] which gave the δ-C(sp^2)-H alkenylated derivative **24a** in 88% yield (Scheme 9).



Scheme 9. Pd(II)-catalyzed, MICA-aided δ-C(sp^2)-H amidation/alkenylation of phenethylamine derivatives **22**.



Scheme 10. Gram scale reaction and DG removal trials.

Furthermore, we also performed the Pd(II)-catalyzed, MICA-aided γ-C(sp^3) arylation reaction in a gram scale (Scheme 10). Accordingly, the treatment of a mixture of MICA-based substrate **11d**, 1-iodo-3-nitrobenzene, $Pd(OAc)_2$ catalyst and AgOAc additive at 110 °C for 24 h afforded the product **12k** in 45% yield (0.67 g, Scheme 10). Next, we intended to show the removal of the MICA DG after the γ-C(sp^3)-arylation of **11**. In this regard, a few exemplary reactions comprising the removal of the MICA DG are shown in Scheme 10. At first, we performed the base-mediated hydrolysis of the substrates **12o/12a**, which afforded the 2-aminodiphenylmethane derivatives **25a,b** in 35-50% yields.

Then, the treatment of the substrates **12b,k** with the $(Boc)_2O$ reagent gave the *N*-Boc derivatives **26a,c** in 65-77% yields, respectively. Subsequently, the treatment of the substrates **26a,c** with K_2CO_3 has led to the removal of the MICA DG from the substrates **26a,c** and gave the *N*-Boc 2-aminodiphenylmethane derivatives **26b,d** in 65-70% yields, respectively (Scheme 10). Removal of the Boc group from **26d** in the presence of TFA afforded the 2-aminodiphenylmethane derivative **26e** in 70% yield. Next, we wished to reveal the utility of the 2-aminodiphenylmethane derivatives (**25a,b** and **26e**). In this regard, the 2-aminodiphenylmethane derivatives **25b** and **26e** were treated with glucose under the reaction conditions reported in a patent work,[11b,c] which targeted the construction of hsGLT2 inhibitor motif (**3f**, Figure 2). Accordingly, the treatment of **25b** and **26e** with glucose afforded the corresponding *N*-glucoside motifs **27a,b** in 30-46% yields (as diastereomers with *dr* up to 88:12, Scheme 10).

Conclusions:

In summary, we have reported a dual objective-based study comprising exploration of the Pd(II)-catalyzed sp^3/sp^2 γ- and δ-C-H functionalization of aryl amines using 5-methylisoxazole-3-carboxamide (MICA) as a DG and construction of various MICA motifs. The MICA-aided γ-C(sp^3)-H arylation of *ortho*-toluidine derivatives **11** with heteroaryl iodides was useful for assembling various 2-aminodiphenylmethanes **12**. The structure of a representative arylheteroarylmethane compound **12b** was confirmed by the X-ray structure analysis (Figure 3).[12]

While extensive optimizations did not help to improve the efficiency of the γ-C(sp^3)-H arylation of **11**, continuous efforts will be made to improve the efficiency. The MICA-aided γ-C(sp^3)-H acetoxylation of **11** afforded various 2-aminobenzyl acetates in good yields. Similarly, the MICA-aided γ-C(sp^2)-H arylation/acetoxylation of benzylamine derivatives **19** gave various *ortho* C-H arylated/acetoxylated products **20** and **21** in good yields. We have shown the MICA-aided remote δ-C(sp^2)-H amidation/alkenylation of phenethylamine derivatives **22**. Control reactions were performed to assess the relative effectiveness of MICA-aided γ-C(sp^3)-H arylation.[13] We have also shown that the MICA is a removable DG. Apart

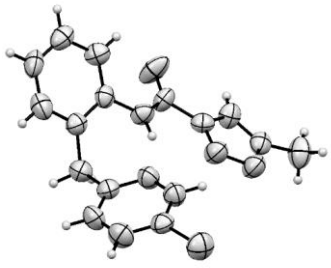


Figure 3. X-ray (ORTEP) structure of **12b**.

from the usage of MICA as a DG for the sp^2/sp^3 C-H functionalization of aryl amines, indirectly this work has led to the construction of a library of new MICA motifs. This is an added advantage to note that in general, MICA-based motifs have received considerable attention in medicinal chemistry.

Experimental Section

General. TLC analyses were performed using silica gel for TLC or silica gel 60 F_{254} pre-coated plates and visualized by observation under iodine vapor or irradiation with UV lamp. Reactions were done using oven-dried round-bottom flasks in anhydrous solvents under a nitrogen atm. The column chromatography purification was performed using silica gel (100-200 mesh) or neutral alumina (eluent = combination of ethyl acetate and hexanes). ^{1}H NMR and ^{13}C{^{1}H} NMR spectra of samples have been recorded on 400 and 101 MHz spectrometers, respectively (using TMS as an internal standard). The HRMS data were obtained from QTOF mass analyzer using electrospray ionization (ESI) method. The IR spectra of samples have been recorded either as neat samples or using KBr pellets or in an appropriate solvent. Isolated yields of the products were reported and yields were not optimized. In the reactions involving γ-C(sp^3)-H arylation of **11a-f**, while the formation of the corresponding ketones (arylation-oxidation) products cannot be completely ignored, apart from the corresponding products **12**, we did not isolate any other side-products in characterizable amounts to the best of our effort. In most of the cases, the recovery of the corresponding starting compounds was noted based on TLC or the NMR spectra of the crude reaction mixtures. Starting compounds **9b**[a], **9c**[b], **9a**[c], **9d**[d] and **9e**[e] are known compounds in the literature.

References:

[a] S. A. Rzhevskiy, A. A. Ageshina, G. A. Chesnokov, P. S. Gribanov, M. A. Topchiy, M. S. Nechaev, A. F. Asachenko, *RSC Adv.* **2019**, *9*, 1536.

[b] X.-Y. Qian, S.-Q. Li, J. Song, H.-C. Xu, *ACS Catal.* **2017**, *7*, 2730.

[c] Y. Xie, Y. Yang, L. Huang, X. Zhang, Y. Zhang, *Org. Lett.* **2012**, *14*, 1238

[d] M. de L. F. Bispo, R. S. B. Gonçalves, C. H. da S. Lima, L. N. de F. Cardoso, M. C. S. Lourenço, M. V. N. de Souza, *J. Heterocyclic Chem.* **2012**, *49*, 1317.

[e] L. Ju, J. Yao, Z. Wu, Z. Liu, Y. Zhang, *J. Org. Chem.* **2013**, *78*, 10821.

General procedures for the preparation of carboxamides: An appropriate amount of carboxylic 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 atm, then an appropriate amount of amine (1 equiv) was added to the above mixture and stirred for 16-24 h at rt. Then, the resulting solution was subjected to aqueous workup and washed with aqueous sodium bicarbonate solution (two times). Then, the resulting solution mixture was concentrated and purified on silica gel column chromatography (eluent=EtOAc:Hexanes) to give the corresponding carboxamides.

General procedures for the Pd(II)-catalyzed arylation of MICA-based carboxamides: An appropriate carboxamide (0.2 mmol, 1 equiv), an appropriate aryl iodide (0.6 mmol, 3 equiv), $Pd(OAc)_2$ (10 mol%) and AgOAc (2.2 equiv) in anhydrous toluene (2 mL) was heated at 110 ^{o}C for 24 h under a nitrogen atm. After the reaction period, the reaction mixture was concentrated in vacuum and purification of the resulting reaction mixture by column chromatography on silica gel (eluent=EtOAc:Hexanes) gave the corresponding arylated carboxamides (see the corresponding Tables/Schemes for specific entries).

General procedures for the Pd(II)-catalyzed acetoxylation of MICA-based carboxamides: A RB flask containing a mixture of an appropriate carboxamide (0.2 mmol), $Pd(OAc)_2$ (10 mol%), $PhI(OAc)_2$ (1.5 equiv), Ac_2O (1 equiv) and AcOH (1 equiv) in toluene (2 mL) was heated at 130 ^{o}C for 24 h. Then, the reaction mixture was cooled to rt and concentrated under reduced pressure to afford a crude reaction mixture, which was purified by column chromatography on silica gel to give the desired product (see the corresponding Tables/Schemes for specific entries).

Typical procedure for the conversion of 12b into 26a:

A solution of **12b** (0.14 mmol) in acetonitrile (5 mL), $(Boc)_2O$ (5.0 equiv) and DMAP (2 equiv) was heated at 55 ^{o}C for 8 h. Then, the reaction mixture was diluted with DCM (10 mL) and washed with brine solution twice. Then, the resulting organic layers were dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to afford a crude reaction mixture, which was purified by column chromatography on silica gel to give the product **26a**. Using this procedure, the compound **26c** was obtained from **12k**.

Typical procedure for the conversion of 26a into 26b:

To a solution of **26a** in methanol (2 mL), K_2CO_3 (2 equiv) was added at 0 ^{o}C and the reaction mixture was allowed to attain the rt and stirred for 12 h. Then, the reaction mixture was

quenched by the addition of 0.5 N HCl (2 mL) and stirred for a further 5 min. The resulting solution was dissolved in ethyl acetate and washed with saturated sodium bicarbonate solution, water, and brine. Then, the resulting organic layers were dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to afford a crude reaction mixture, which was purified by column chromatography on silica gel to give the product **26b**. Using this procedure, the compound **26d** was obtained from **26c**. Apart from the **26b**/**26d**, the corresponding DG part, methyl 5-methylisoxazole-3-carboxylate was also isolated (around in 60% yield) in these reactions.

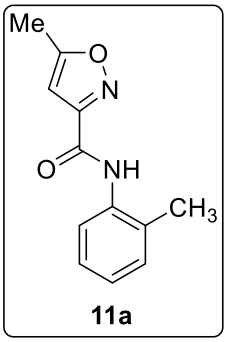
Typical procedure for the preparation of 27a:[11c] To a solution of **25b** (0.2 mmol) in MeOH (1 mL), D-(+)-glucose (0.25 mmol) and NH_4Cl (0.2 equiv) were added. The solution was refluxed for 4 h, after the reaction time, the reaction mixture was concentrated under reduced pressure and the crude reaction mixture was purified by silica gel chromatography to give the product **27a**.

Typical procedure for the preparation of 27b:[11c] A solution of **26e** (0.18 mmol) in EtOH (2 mL) and D-(+)-glucose (0.25 mmol) was refluxed for 24 h. After the reaction time, the reaction mixture was concentrated under reduced pressure and the crude reaction mixture was purified by silica gel chromatography to give the product **27b**.

Typical procedure for the conversion of 26d into 26e:

To a solution of **26d** in dichloromethane (2 mL), TFA (2 mL) was added at 0 ^oC and then, the reaction mixture was allowed to attain the rt and stirred at rt for 2 h (the reaction performed in open atmosphere as CO_2 gas evolved in this reaction). Then, the reaction mixture was concentrated and diluted with ethyl acetate, then washed with sodium bicarbonate solution, water, and brine. The resulting organic layers were dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to afford a crude reaction mixture, which was purified by column chromatography on silica gel to give the product **26e**.

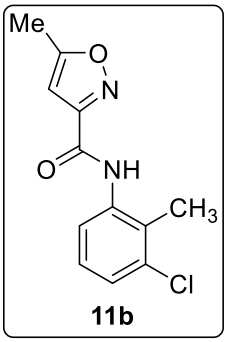
5-Methyl-*N*-(*o*-tolyl)isoxazole-3-carboxamide (11a): The compound was obtained after purification by column chromatography on silica gel (EtOAc:Hexanes = 20:80) as a colourless solid; Yield: 68% (740 mg, 5 mmol scale), mp: 72-74 ^oC, R_f = 0.50, IR (DCM): 3402, 1705, 1590, 1453 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 8.50 (br s, 1H), 8.02 (d, J = 8.0 Hz, 1H), 7.28-7.23 (m, 2H), 7.15-7.11 (m, 1H), 6.53 (s, 1H), 2.50 (s, 3H), 2.36 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 171.7, 159.1, 156.9, 135.0, 130.6, 128.9, 126.9,



11a

125.5, 122.5, 101.6, 17.6, 12.4; HRMS (ESI): *m/z* [M + Na]$^+$ calcd for $C_{12}H_{12}N_2NaO_2$: 239.0796; found 239.0787.

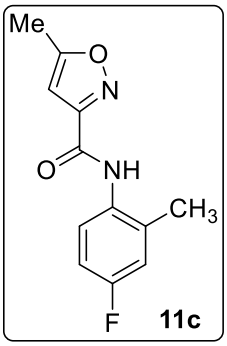
***N*-(3-Chloro-2-methylphenyl)-5-methylisoxazole-3-carboxamide (11b):** The compound



11b

was obtained after purification by column chromatography on silica gel (EtOAc:Hexanes = 20:80) as a colourless solid; Yield: 77% (578 mg, 3 mmol scale), mp:112-124 ^{o}C, R_f = 0.50, IR (DCM): 3333, 3158, 1679, 1462 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.53 (br s, 1H), 7.86 (d, J = 8.0 Hz, 1H), 7.26 (d, J = 8.0 Hz, 1H), 7.18 (t, J = 8.0 Hz, 1H), 6.53 (s, 1H), 2.52 (s, 3H), 2.39 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 171.8, 158.8, 157.1, 136.0, 135.0, 128.1, 127.1, 126.6, 121.7, 101.6, 14.5, 12.4. HRMS (ESI): *m/z* [M + H]+ calcd for $C_{12}H_{12}ClN_2O_2$: 251.0587; found 251.0575.

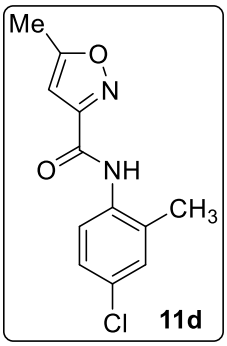
***N*-(4-Fluoro-2-methylphenyl)-5-methylisoxazole-3-carboxamide (11c):** The compound



11c

was obtained after purification by column chromatography on silica gel (EtOAc:Hexanes = 20:80) as a colourless solid; Yield: 45% (313 mg, 3 mmol scale); mp: 114-116 ^{o}C, R_f = 0.50, IR (DCM): 3402, 1696, 1531, 875 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.37 (br s, 1H), 7.88 (dd, J_1 = 9.7 Hz, J_2 = 5.5 Hz, 1H), 6.97-6.93 (m, 2H), 6.54 (s, 1H), 2.53 (s, 3H), 2.35 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 171.8, 160.1 (d, J = 242 Hz), 157.1, 132.8 (d, J = 8 Hz), 130.7, 130.7, 124.7 (d, J = 8.3 Hz), 117.2 (d, J = 22.3 Hz), 113.4 (d, J = 22.1 Hz), 101.6, 17.8 (d, J = 0.9 Hz), 12.4; HRMS (ESI): *m/z* [M + H]$^+$ calcd for $C_{12}H_{12}FN_2O_2$: 235.0883; found 235.0871.

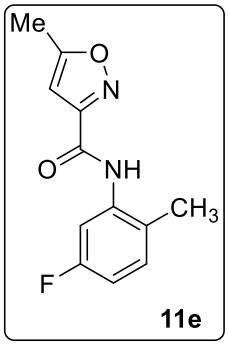
***N*-(4-Chloro-2-methylphenyl)-5-methylisoxazole-3-carboxamide (11d):** The compound



11d

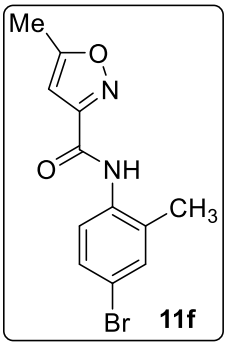
was obtained after purification by column chromatography on silica gel (EtOAc:Hexanes = 20:80) as a colourless solid; Yield: 54% (678 mg, 5 mmol scale), mp: 124-126 ^{o}C, R_f = 0.50, IR (DCM): 3397, 1701, 1592, 817 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.45 (br s, 1H), 7.95- 7.92 (m, 1H), 7.20-7.17 (m, 2H), 6.48 (s, 1H), 2.49 (s, 3H), 2.30 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 171.8, 158.8, 156.9, 133.6, 130.8, 130.3, 126.7, 123.6, 101.5, 17.5, 12.4; HRMS (ESI): *m/z* [M + H]$^+$ calcd for $C_{12}H_{12}ClN_2O_2$: 251.0587; found 251.0594.

***N*-(5-Fluoro-2-methylphenyl)-5-methylisoxazole-3-carboxamide (11e):** The compound



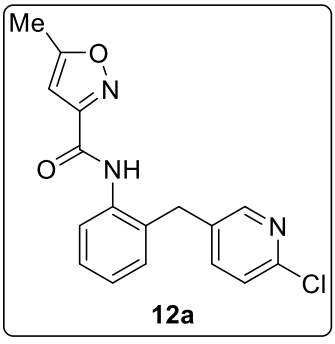
was obtained after purification by column chromatography on silica gel (EtOAc:Hexanes = 20:80) as a colourless solid; Yield: 56% (660 mg, 5 mmol scale); mp: 124-126 ºC, R_f = 0.50, IR (DCM): 3398, 1704, 1547, 819 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 8.51 (br s, 1H), 8.0 (dd, J_1 = 10.8 Hz, J_2 = 2.4 Hz, 1H), 7.17 (t, J = 7.3 Hz, 1H), 6.82 (td, J_1 = 8.2 Hz, J_2 = 2.5 Hz, 1H), 6.55 (s, 1H), 2.54 (s, 3H), 2.33 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 171.9, 161.3 (d, J = 241.5 Hz), 158.9 ,156.8, 136.0 (d, J = 11.1 Hz), 131.2 (d, J = 8.8 Hz), 122.8 (d, J = 3.3 Hz), 111.6 (d, J = 21.1 Hz), 108.9 (d, J = 26.9 Hz), 101.5, 16.9, 12.4; HRMS (ESI): *m/z* $[M + Na]^+$ calcd for $C_{12}H_{11}FN_2NaO_2$: 257.0702; found 257.0692.

***N*-(4-Bromo-2-methylphenyl)-5-methylisoxazole-3-carboxamide (11f):** The compound



was obtained after purification by column chromatography on silica gel (EtOAc:Hexanes = 20:80) as a colourless solid; Yield: 35% (307 mg, 3 mmol scale); mp: 122-124 ºC, R_f = 0.50, IR (DCM): 3395, 1703, 1537, 817 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 8.44 (br s, 1H), 7.92 (d, J = 9.2 Hz, 1H), 7.35-7.34 (m, 2H), 6.50 (s, 1H), 2.51 (s, 3H), 2.31 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 171.8, 158.9, 156.9, 134.1, 133.2, 130.9, 129.8, 123.8, 118.2, 101.5, 17.4, 12.4; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{12}H_{12}BrN_2O_2$: 295.0082; found 295.0070.

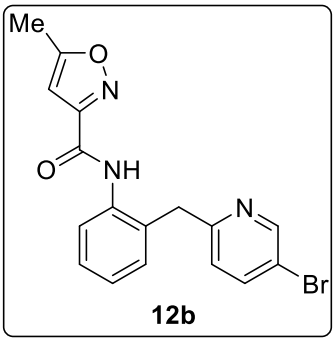
***N*-(2-((6-Chloropyridin-3-yl)methyl)phenyl)-5-methylisoxazole-3-carboxamide (12a):**
The compound was obtained after purification by column chromatography on silica gel



(EtOAc:Hexanes = 20:80) as a colourless solid; Yield: 50% (33 mg); mp: 120-122 ºC, R_f = 0.20, IR (DCM): 3387, 1688, 1456, 818 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 8.34 (br s, 1H), δ 8.31 (d, J = 2.1 Hz, 1H), 7.89 (d, J = 8.0 Hz, 1H), 7.46 (dd, J_1 = 8.2 Hz, J_2 = 2.5 Hz, 1H), 7.38- 7.34 (m, 1H), 7.26-7.20 (m, 3H), 6.51 (d, J = 0.76 Hz, 1H), 4.03 (s, 2H), 2.52 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 171.9, 158.7, 157.2, 149.8, 149.8, 139.1, 134.4, 133.5, 131.5, 130.6, 128.2, 126.5, 124.5, 124.3, 101.5, 34.4, 12.4; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{17}H_{15}ClN_3O_2$: 328.0853; found 328.0862.

***N*-(2-((5-Bromopyridin-2-yl)methyl)phenyl)-5-methylisoxazole-3-carboxamide (12b):**

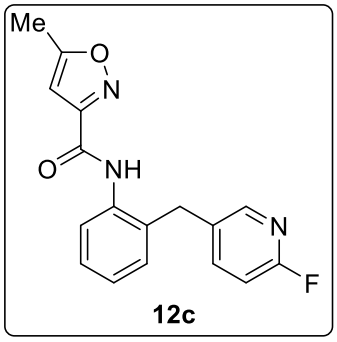
The compound was obtained after purification by column chromatography on silica gel



12b

(EtOAc:Hexanes = 20:80) as a colourless solid; Yield: 42% (23 mg); mp:169-171 ^{o}C, R_f = 0.45, IR (DCM): 3054, 1681, 1594, 1460 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 11.74 (br s, 1H), 8.69 (s, 1H), 8.06 (d, J = 8.0 Hz, 1H), 7.76 (d, J = 8.2 Hz, 1H), 7.33-7.29 (m, 2H), 7.20 (d, J = 8.2 Hz, 1H), 7.13 (t, J = 7.5 Hz, 1H), 6.57 (s, 1H), 4.11 (s, 2H), 2.54 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 171.0, 159.9, 159.0, 157.9, 150.1, 140.1, 136.1, 131.0, 130.2, 127.8, 125.4, 124.5, 124.0, 118.7, 101.8, 41.0, 12.4. HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{17}H_{15}BrN_3O_2$: 372.0348; found 372.0334.

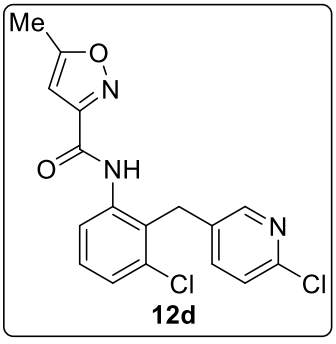
***N*-(2-((6-Fluoropyridin-3-yl)methyl)phenyl)-5-methylisoxazole-3-carboxamide (12c):** The compound was obtained after purification by column chromatography on silica gel



12c

(EtOAc:Hexanes = 20:80) as a colourless solid; Yield: 35% (21 mg); mp: 94-96 ^{o}C, R_f = 0.30, IR (DCM): 3286, 1693, 1533, 1484 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.35 (br s, 1H), 8.13 (s, 1H), 7.91 (d, J = 7.9 Hz, 1H), 7.59 (td, J_1 = 8.1 Hz, J_2 = 2.5 Hz, 1H), 7.39-7.34 (m, 1H), 7.27- 7.22 (m, 2H), 6.87 (dd, J_1 = 8.4 Hz, J_2 = 3.0 Hz, 1H), 6.51 (s, 1H), 4.05 (s, 2H), 2.53 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 171.8, 162.6 (d, J = 237.0 Hz), 158.7, 157.2, 147.4 (d, J = 14.5 Hz), 141.5 (d, J = 7.7 Hz), 134.5, 132.1 (d, J = 4.6 Hz), 131.6, 130.5, 128.1, 126.4, 124.4, 109.6 (d, J = 37.1 Hz), 101.4, 34.2, 12.4; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{17}H_{15}FN_3O_2$: 312.1148; found 312.1134.

***N*-(3-Chloro-2-((6-chloropyridin-3-yl)methyl)phenyl)-5-methylisoxazole-3-carboxamide (12d):** The compound was obtained after purification by column chromatography on silica gel

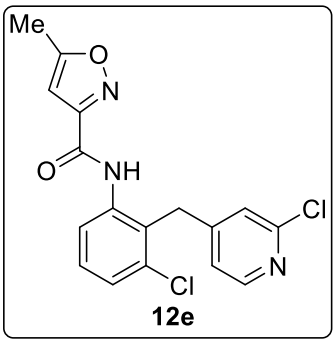


12d

(EtOAc:Hexanes = 20:80) as a colourless solid; Yield: 45% (32 mg); mp: 164-166 ^{o}C, R_f = 0.20, IR (DCM): 3295, 1673, 1575, 1414 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.40 (br s, 1H), 8.35 (d, J = 2.3 Hz, 1H), 7.91-7.90 (m, 1H), 7.48 (dd, J_1 = 8.2 Hz, J_2 = 2.5 Hz, 1H), 7.39-7.31 (m, 2H), 7.24 (d, J = 8.24 Hz, 1H), 6.50 (s, 1H), 4.24 (s, 2H), 2.53 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 172.1, 158.4, 157.3, 149.9, 149.4, 138.5, 136.2, 135.1, 132.3,

129.3, 128.8, 127.3, 124.3, 123.1, 101.4, 31.0, 12.4; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{17}H_{14}Cl_2N_3O_2$: 362.0463; found 362.0480.

***N*-(3-Chloro-2-((2-chloropyridin-4-yl)methyl)phenyl)-5-methylisoxazole-3-carboxamide**

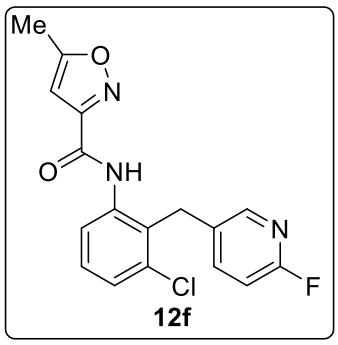


12e

(12e): The compound was obtained after purification by column chromatography on silica gel (EtOAc:Hexanes = 20:80) as a colourless solid; Yield: 40% (28 mg); mp: 112-114 ^oC, R_f = 0.30, IR (DCM): 1692, 1592, 1459, 1385 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 8.34 (br s, 1H), 8.28 (d, J = 2.1 Hz, 1H), 7.88 (d, J = 7.6 Hz, 1H), 7.40-7.33 (m, 2H), 7.18 (s, 1H), 7.07 (s, 1H), 6.49 (s, 1H), 4.26 (s, 2H), 2.52 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 172.0, 158.4, 157.3, 152.1, 150.3, 149.9, 136.4, 135.4, 129.1, 128.7, 127.4, 123.9, 123.3, 122.2, 101.4, 33.6, 12.4; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{17}H_{14}Cl_2N_3O_2$: 362.0463; found 362.0481.

***N*-(3-Chloro-2-((6-fluoropyridin-3-yl)methyl)phenyl)-5-methylisoxazole-3-carboxamide**

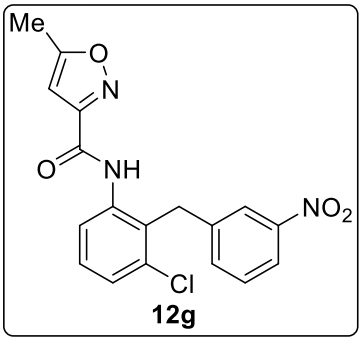
(12f): The compound was obtained after purification by column chromatography on silica gel



12f

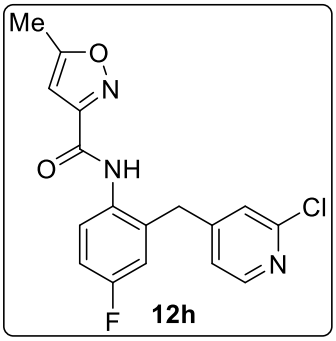
(EtOAc:Hexanes = 20:80) as a colourless solid; mp: 130-132 ^oC, Yield: 40% (27 mg); R_f = 0.20, IR (DCM): 3279, 1696, 1529, 1458 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 8.41 (br s, 1H), 8.17 (d, J = 1.5 Hz, 1H), 7.93 (d, J = 7.8 Hz, 1H), 7.62 (td, J_1 = 8.2 Hz, J_2 = 2.6 Hz, 1H), 7.39- 7.30 (m, 2H), 6.86 (dd, J_1 = 8.4 Hz, J_2 = 3.0 Hz, 1H), 6.50 (s, 1H), 4.26 (s, 2H), 2.52 (s, 3H); ^{13}C NMR (101 MHz, CDCl3): δ 172.0, 162.7 (d, J = 237.0 Hz), 158.5, 157.2, 147.1 (d, J = 14.5 Hz), 140.9 (d, J = 7.8 Hz), 136.2, 135.1, 130.9 (d, J = 4.5 Hz), 129.5, 128.8, 127.3, 122.9, 109.7 (d, J = 37.3 Hz), 101.4, 30.8, 12.4; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{17}H_{14}ClFN_3O_2$: 346.0759; found 346.0744.

***N*-(3-Chloro-2-(3-nitrobenzyl)phenyl)-5-methylisoxazole-3-carboxamide (12g):** The compound was obtained after purification by column chromatography on silica gel (EtOAc:Hexanes = 20:80) as a colourless solid; Yield: 35% (25 mg); mp: 144-146 °C, R_f = 0.30, IR (DCM): 3383, 1696, 1580, 875 cm^{-1};^{1}H NMR (400 MHz, $CDCl_3$): δ 8.36 (br s, 1H), 8.13-8.09 (m, 2H), 7.93 (dd, J_1 = 7.92 Hz, J_2 = 1.08 Hz, 1H), 7.55 (d, J = 7.7 Hz, 1H), 7.47 (t, J = 7.9 Hz, 1H), 7.40 (dd, J_1 = 8.1 Hz, J_2 = 1.28 Hz, 1H), 7.34 (t, J = 8.0 Hz, 1H), 6.48 (s, 1H), 4.38 (s, 2H), 2.51 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 172.0, 158.5, 157.2, 148.5, 139.8, 136.4, 135.2, 134.3 129.8, 129.4, 128.9, 127.3, 123.3, 123.0, 122.0, 101.4, 34.1, 12.4. HRMS (ESI): *m/z* [M + Na]$^+$ calcd for $C_{18}H_{14}ClN_3NaO_4$: 394.0571; found 394.0555.



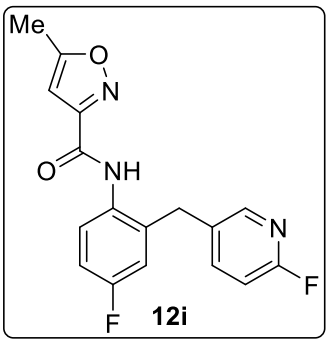
12g

***N*-(2-((2-Chloropyridin-4-yl)methyl)-4-fluorophenyl)-5-methylisoxazole-3-carboxamide (12h):** The compound was obtained after purification by column chromatography on silica gel (EtOAc:Hexanes = 20:80) as a colourless coloured solid; Yield: 45% (30. mg); mp: 132-134 °C, R_f = 0.30; IR (DCM): 3279, 2923, 1693, 1457 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.30 (d, J = 5.1 Hz, 1H), 8.22 (br s, 1H), 7.75 (dd, J_1 = 8.8 Hz, J_2 = 5.3 Hz, 1H), 7.17 (s, 1H), 7.10- 7.04 (m, 2H), 6.95 (dd, J_1 = 8.9 Hz, J_2 = 2.9 Hz, 1H), 6.49 (s, 1H), 4.00 (s, 2H), 2.52 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 171.9, 160.7 (d, J = 245.6 Hz), 158.4, 157.5, 152.1, 150.7, 150.0, 133.9 (d, J = 7.5 Hz), 130.4 (d, J = 3.0 Hz), 127.3 (d, J = 8.5 Hz), 124.4, 122.7, 117.5 (d, J = 22.9 Hz), 115.1 (d, J = 22.1 Hz), 101.5, 37.4, 12.4; HRMS (ESI): *m/z* [M + H]$^+$ calcd for $C_{17}H_{14}ClFN_3O_2$: 346.0759; found 346.0743.



12h

***N*-(4-Fluoro-2-((6-fluoropyridin-3-yl)methyl)phenyl)-5-methylisoxazole-3-carboxamide (12i):** The compound was obtained after purification by column chromatography on silica gel (EtOAc:Hexanes = 20:80) as a colourless solid; Yield: 42% (27 mg); mp: 112-114 °C, R_f = 0.25; IR (DCM): 3387, 3056, 1696, 1460 cm^{-1}; ^{1}H NMR (400 MHz, CDCl3): δ 8.30 (br s, 1H), 8.11 (s, 1H), 7.77 (dd, J_1 = 8.6 Hz, J_2 = 5.4 Hz, 1H), 7.60 (t, J = 8.0 Hz, 1H), 7.07-7.03 (m, 1H), 6.92-6.88 (m, 2H), 6.50 (s, 1H), 4.01 (s, 2H), 2.52 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 171.9, 162.7 (d, J = 237.4 Hz), 160.7 (d, J = 245.5 Hz), 158.5, 157.5 147.5 (d, J =

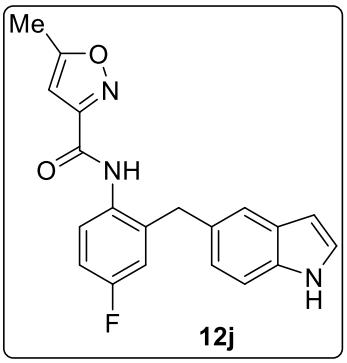


12i

14.6 Hz), 141.5 (d, *J* = 7.9 Hz), 135.1 (d, *J* = 7.6 Hz), 131.4 (d, *J* = 4.5 Hz), 130.2 (d, *J* = 2.8 Hz), 126.9 (d, *J* = 8.4 Hz), 117.1 (d, *J* = 22.9 Hz), 114.8 (d, *J* = 22.1 Hz), 109.8 (d, *J* = 37.2 Hz), 101.5, 34.1, 12.4. HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{17}H_{14}F_2N_3O_2$: 330.1054; found 330.1038.

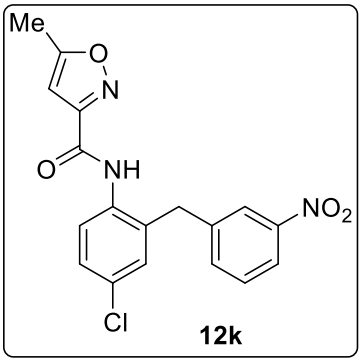
***N*-(2-((1*H*-Indol-5-yl)methyl)-4-fluorophenyl)-5-methylisoxazole-3-carboxamide (12j):**

The compound was obtained after purification by column chromatography on silica gel (EtOAc:Hexanes = 20:80) as a yellow coloured solid; Yield: 35% (24 mg); mp: 139-141 °C, R_f = 0.30; IR (DCM): 3354, 1683, 1596, 1456 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 8.47 (br s, 1H), 8.23 (br s, 1H), 7.95-7.79 (m, 1H), 7.52 (s, 1H), 7.36 (d, *J* = 8.3 Hz, 1H), 7.21 (t, *J* = 2.8 Hz, 1H), 7.06 (dd, *J1* = 8.4 Hz, *J2* = 1.4 Hz, 1H), 7.03-6.99 (m, 2H), 6.53 (s, 1H), 6.47 (s, 1H), 4.12 (s, 2H), 2.50 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 171.5, 160.2 (d, *J* = 243.0 Hz), 158.9, 157.3, 136.1 (d, *J* = 7.4 Hz), 134.8, 130.7 (d, *J* = 2.9 Hz), 129.0, 128.3, 125.4 (d, *J* = 8.4 Hz), 124.7, 123.1, 120.8, 117.3 (d, *J* = 22.7 Hz), 113.7 (d, *J* = 22.2 Hz), 111.6, 102.5, 101.5, 38.2, 12.4; HRMS (ESI): *m/z* $[M + Na]^+$ calcd for $C_{20}H_{16}FN_3NaO_2$: 372.1124; found 372.1108.



12j

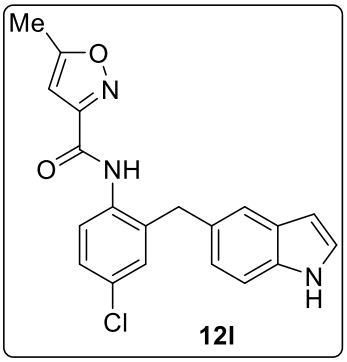
***N*-(4-Chloro-2-(3-nitrobenzyl)phenyl)-5-methylisoxazole-3-carboxamide (12k):** The compound was obtained after purification by column chromatography on silica gel (EtOAc:Hexanes = 20:80) as a yellow coloured solid; Yield: 50% (37 mg); mp: 144-146 °C, R_f = 0.35; IR (DCM): 3377, 1697, 1528, 812 cm^{-1}; ^1H NMR (400 MHz, CDCl3): δ 8.28 (br s, 1H), 8.13-8.11 (m, 2H), 7.91 (d, *J* = 8.6 Hz, 1H), 7.56-7.49 (m, 2H), 7.35 (dd, J_1 = 8.6 Hz, J_2 = 2.4 Hz, 1H), 7.26 (d, *J* = 2.3 Hz, 1H), 6.48 (s, 1H), 4.13 (s, 2H), 2.52 (s, 3H); ^{13}C NMR (101 MHz, CDCl3): δ 172.0, 158.4, 157.1, 148.5, 140.0, 134.9, 133.2, 133.1, 131.5, 130.6, 129.9, 128.3, 125.5, 123.8, 122.2, 101.4, 37.6, 12.4; HRMS (ESI): *m/z* $[M + Na]^+$ calcd for $C_{18}H_{14}ClN_3NaO_4$: 394.0571; found 394.0570.



12k

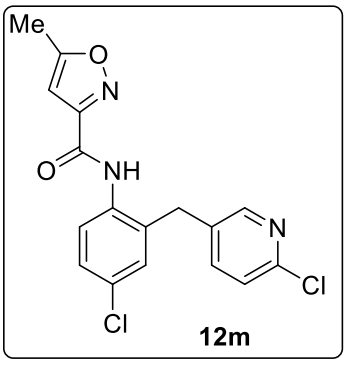
***N*-(2-((1*H*-Indol-5-yl)methyl)-4-chlorophenyl)-5-methylisoxazole-3-carboxamide (12l):**

The compound was obtained after purification by column chromatography on silica gel (EtOAc:Hexanes = 20:80) as a colourless solid; Yield: 35% (23 mg); mp: 144-146 ºC, R_f = 0.30, IR (DCM): 3355, 2921, 1694, 1595 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.55 (br s, 1H), 8.20 (br s, 1H), 8.04 (d, J = 8.3 Hz, 1H), 7.53 (s, 1H), 7.37 (d, J = 8.3 Hz, 1H), 7.30 (d, J = 9.8 Hz, 1H), 7.22 (s, 1H), 7.07 (d, J = 8.4 Hz, 1H), 6.54 (s, 1H), 6.45 (s, 1H), 4.11 (s, 2H), 2.50 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 171.5, 158.8, 157.2, 134.9, 134.6, 133.6, 130.5, 130.4, 128.8, 128.3, 127.2, 124.7, 124.3, 123.0, 120.8, 111.6, 102.6, 101.4, 38.2, 12.4; HRMS (ESI): *m/z* [M + Na]$^+$ calcd for $C_{20}H_{16}ClN_3NaO_2$: 388.0829; found 388.082.



12l

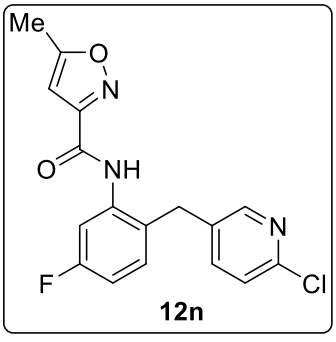
***N*-(4-Chloro-2-((6-chloropyridin-3-yl)methyl)phenyl)-5-methylisoxazole-3-carboxamide**



12m

(12m): The compound was obtained after purification by column chromatography on silica gel (EtOAc:Hexanes = 20:80) as a colourless solid; Yield: 35% (24 mg); mp: 154-156 ºC, R_f = 0.30; IR (DCM): 3384, 1685, 1527, 1459 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.32-8.31 (m, 2H), 7.87 (d, J = 8.6 Hz, 1H), 7.47 (dd, J_1 = 8.2 Hz, J_2 = 2.5 Hz, 1H), 7.33 (dd, J_1= 8.6 Hz, J_2 = 2.4 Hz, 1H), 7.29-7.27 (m, 1H), 7.20 (d, J = 2.3 Hz, 1H), 6.50 (s, 1H), 4.00 (s, 2H), 2.53 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 172.0, 158.4, 157.2, 150.2, 149.8, 139.1, 133.1, 133.0, 132.5, 131.6, 130.3, 128.2, 125.6, 124.5, 101.4, 34.2, 12.5. HRMS (ESI): *m/z* [M + H]$^+$ calcd for $C_{17}H_{14}Cl_2N_3O_2$: 362.0463; found 362.0451.

***N*-(2-((6-Chloropyridin-3-yl)methyl)-5-fluorophenyl)-5-methylisoxazole-3-carboxamide**

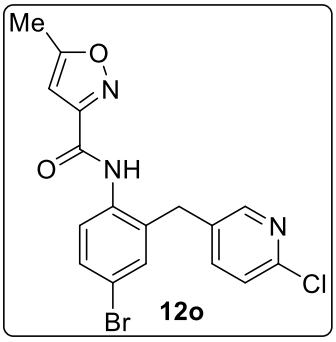


12n

(12n): The compound was obtained after purification by column chromatography on silica gel (EtOAc:Hexanes = 20:80) as a yellow coloured solid; Yield: 35% (23 mg); mp: 136-138 ºC, *Rf* = 0.30. IR (DCM): 3398, 2975, 1697, 1493 cm^{-1} ; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.42 (br s, 1H), 8.32 (d, J = 1.5 Hz, 1H), 7.90 (dd, J_1 = 10.4 Hz, J_2 = 2.4 Hz, 1H), 7.46 (dd, J_1 = 8.2 Hz, J_2 = 2.0 Hz, 1H), 7.28-7.26 (m, 1H), 7.19 (dd, J_1 = 8.0 Hz, J_2 = 6.5 Hz, 1H), 6.93 (td, J_1 = 8.1 Hz, J_2 = 2.3

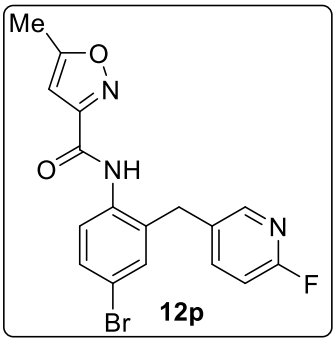
Hz, 1H), 6.51 (s, 1H), 4.01 (s, 2H), 2.53 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 172.1, 162.0 (d, J = 244.1 Hz), 158.5, 157.0, 150.1, 149.7, 139.0, 135.8 (d, J = 11.0 Hz), 132.9, 131.5 (d, J = 9.2 Hz), 125.4 (d, J = 3.5 Hz), 124.4, 112.6 (d, J = 21.3 Hz), 110.8 (d, J = 26.2 Hz), 101.4, 33.8, 12.4; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{17}H_{14}ClFN_3O_2$: 346.0759; found 346.0746.

***N*-(4-Bromo-2-((6-chloropyridin-3-yl)methyl)phenyl)-5-methylisoxazole-3-carboxamide**



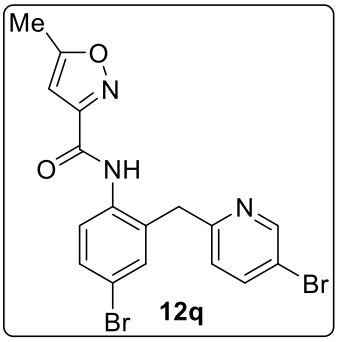
(12o): The compound was obtained after purification by column chromatography on silica gel (EtOAc:Hexanes = 20:80) as a colourless solid; Yield: 42% (33 mg); mp: 148-150 ^{o}C, R_f = 0.25; IR (DCM): 3388, 2985, 1699, 1593 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.37 (br s, 1H), 8.30 (d, J = 2.1 Hz, 1H), 7.80 (d, J = 8.6 Hz, 1H), 7.47-7.45 (m, 2H), 7.34 (d, J = 2.1 Hz, 1H), 7.26 (d, J = 8.2 Hz, 1H), 6.47 (s, 1H), 3.98 (s, 2H), 2.51 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 172.0, 158.4, 157.2, 150.2, 149.7, 139.1, 133.6, 133.4, 133.2, 132.6, 131.2, 125.9, 124.4, 119.4, 101.4, 34.1, 12.4. HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{17}H_{14}BrClN_3O_2$: 405.9958; found 405.9958.

***N*-(4-Bromo-2-((6-fluoropyridin-3-yl)methyl)phenyl)-5-methylisoxazole-3-carboxamide**



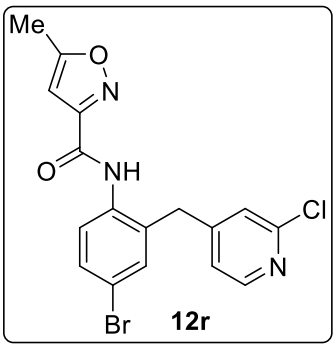
(12p): The compound was obtained after purification by column chromatography on silica gel (EtOAc:Hexanes = 20:80) as a colourless solid; Yield: 42% (32 mg); mp: 132-135 ^{o}C, R_f = 0.20; IR (DCM): 3386, 2987, 1699, 1596 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.33 (br s, 1H), 8.15-8.14 (m, 1H), 7.86 (d, J = 8.6 Hz, 1H), 7.60 (td, J_1 = 8.2 Hz, J_2 = 2.6 Hz, 1H), 7.49 (dd, J_1 = 8.6 Hz, J_2 = 2.3 Hz, 1H), 7.37 (d, J = 2.2 Hz, 1H), 6.90 (dd, J_1 = 8.4 Hz, J_2 = 3.0 Hz, 1H), 6.50 (s, 1H), 4.01 (s, 2H), 2.53 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 172.0, 162.8 (d, J = 237.1 Hz), 158.5, 157.1, 147.4 (d, J = 14.6 Hz), 141.4 (d, J = 7.8 Hz), 133.6, 133.4, 133.2, 131.1, 125.7, 119.3, 109.8 (d, J = 37.3 Hz), 101.4, 34.0, 12.4; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{17}H_{14}BrFN_3O_2$: 390.0253; found 390.0236.

***N*-(4-Bromo-2-((5-bromopyridin-2-yl)methyl)phenyl)-5-methylisoxazole-3-carboxamide**

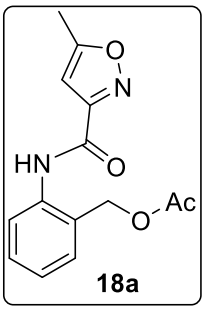


(12q): The compound was obtained after purification by column chromatography on silica gel (EtOAc:Hexanes = 20:80) as a colourless solid; Yield: 37% (31 mg); mp: 210-212 ^{o}C, R_f = 0.30; IR (DCM): 1687, 1580, 1458, 1014 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 11.8 (br s, 1H), 8.70 (s, 1H), 7.96 (d, J = 8.5 Hz, 1H), 7.80 (d, J = 8.2 Hz, 1H), 7.42 (d, J = 12.8 Hz, 2H), 7.21 (d, J = 8.2 Hz, 1H), 6.56 (s, 1H), 4.06 (s, 2H), 2.54 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 171.2, 159.7, 158.2, 158.0, 150.2, 140.3, 135.3, 132.9, 132.9, 130.7, 126.0, 124.1, 119.0, 117.9, 101.7, 40.6, 12.4; HRMS (ESI): *m/z* [M + H]$^{+}$ calcd for $C_{17}H_{14}Br_2N_3O_2$: 449.9453; found 449.9433.

***N*-(4-Bromo-2-((2-chloropyridin-4-yl)methyl)phenyl)-5-methylisoxazole-3-carboxamide**



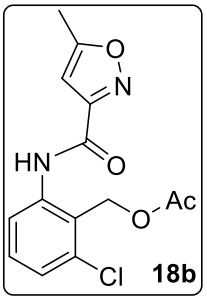
(12r): The compound was obtained after purification by column chromatography on silica gel (EtOAc:Hexanes = 20:80) as a colourless solid; Yield: 44% (35 mg); mp: 144-146 ^{o}C, R_f = 0.20; IR (DCM): 2925, 1695, 1593, 1459 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.30-8.27 (m, 2H), 7.81 (d, J = 8.6 Hz, 1H), 7.50 (dd, J_1 = 8.6 Hz, J_2 = 2.3 Hz, 1H), 7.38 (d, J = 2.2 Hz, 1H), 7.17 (d, J = 0.6 Hz, 1H), 7.06 (dd, J_1 = 5.1 Hz, J_2 = 1.4 Hz, 1H), 6.48 (s, 1H), 4.00 (s, 2H), 2.51 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 172.0, 158.4, 157.2, 152.1, 150.4, 150.0, 133.8, 133.5, 132.4, 131.5, 126.1, 124.3, 122.6, 119.5, 101.4, 36.9, 12.4. HRMS (ESI): *m/z* [M + H]$^{+}$ calcd for $C_{17}H_{14}BrClN_3O_2$: 405.9958; found 405.9953.



2-(5-Methylisoxazole-3-carboxamido)benzyl acetate (18a): The compound was obtained

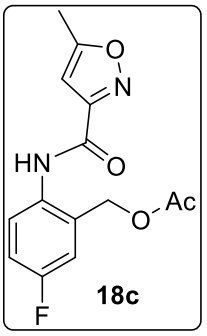
after purification by column chromatography on silica gel (EtOAc:Hexanes = 20:80) as a colourless solid; Yield: 76% (42 mg); mp: 90-92 ^{o}C, R_f = 0.40; IR (DCM): 1744, 1699, 1593, 1456 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.62 (br s, 1H), 8.11 (d, J = 8.1 Hz, 1H), 7.46-7.39 (m, 2H), 7.22 (t, J = 7.4 Hz, 1H), 6.55 (s, 1H), 5.18 (s, 2H), 2.53 (s, 3H), 2.18 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 171.6, 171.2, 159.1, 157.4, 135.9, 130.8, 129.8, 126.5, 125.4, 123.5, 101.5, 64.1, 20.9, 12.4; HRMS (ESI): *m/z* [M + Na]$^{+}$ calcd for $C_{14}H_{14}N_2NaO_4$: 297.0851; found 297.0837.

2-Chloro-6-(5-methylisoxazole-3-carboxamido)benzyl acetate (18b): The compound was



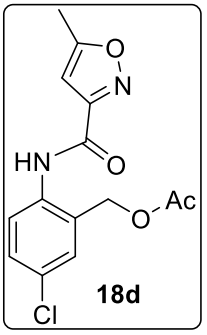
obtained after purification by column chromatography on silica gel (EtOAc:Hexanes = 20:80) as a colourless solid; Yield: 83% (50 mg); mp: 122-124 ^{o}C, R_f = 0.40. IR (DCM): 3271, 1729, 1585, 1463 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 10.19 (br s, 1H), 7.95 (d, J = 8.0 Hz, 1H), 7.36 (t, J = 8.0 Hz, 1H), 7.28 (d, J = 7.5 Hz, 1H), 6.54 (s, 1H), 5.33 (s, 2H), 2.52 (s, 3H), 2.17 (s, 3H): ^{13}C NMR (101 MHz, $CDCl_3$): δ 172.1, 171.6, 159.1, 157.7, 137.7, 136.2, 130.4, 126.6, 125.1, 122.9, 101.5, 60.5, 20.8, 12.4. HRMS (ESI): *m/z* [M + Na]$^{+}$ calcd for $C_{14}H_{13}ClN_2NaO_4$: 331.0462; found 331.0446.

5-Fluoro-2-(5-methylisoxazole-3-carboxamido)benzyl acetate (18c): The compound was



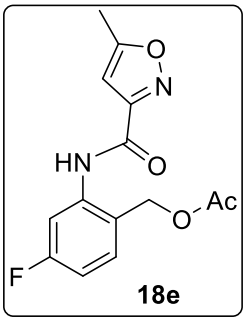
obtained after purification by column chromatography on silica gel (EtOAc:Hexanes = 20:80) as a colourless solid; Yield: 80% (48 mg); mp: 127-129 ^{o}C, R_f = 0.30. IR (DCM): 3379, 1743, 1697, 1495 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.48 (br s, 1H), 7.97 (dd, J_1= 9.8 Hz, J_2 = 5.2 Hz, 1H), 7.13-7.10 (m, 2H), 6.53 (s, 1H), 5.11 (s, 2H), 2.52 (s, 3H), 2.17 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 171.7, 171.1, 159.8 (d, J = 244.5 Hz), 158.9, 157.5, 131.6 (d, J = 2.9 Hz), 129.4 (d, J = 7.3 Hz), 125.8 (d, J = 8.1 Hz), 117.2 (d, J = 23.1 Hz), 116.3 (d, J = 22.0 Hz), 101.5, 63.2, 20.8, 12.4. HRMS (ESI): *m/z* [M + Na]$^{+}$ calcd for $C_{14}H_{13}FN_2NaO_4$: 315.0757; found 315.0741.

5-Chloro-2-(5-methylisoxazole-3-carboxamido)benzyl acetate (18d): The compound was obtained after purification by column chromatography on silica gel (EtOAc:Hexanes = 20:80)



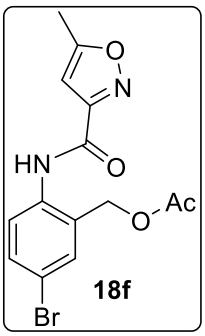
as a colourless solid; Yield: 83% (50 mg); mp: 154-156 ^{o}C, R_f = 0.40. IR (DCM): 3370, 1744, 1701, 1590 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.59 (br s, 1H), 8.05 (d, J = 9.3 Hz, 1H), 7.38- 7.37 (m, 2H), 6.53 (s, 1H), 5.11 (s, 2H), 2.52 (s, 3H), 2.17 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 171.7, 171.1, 158.9, 157.4, 134.4, 130.6, 130.5, 129.7, 128.2, 124.8, 101.5, 63.2, 20.8, 12.4; HRMS (ESI): *m/z* [M + Na]$^{+}$ calcd for $C_{14}H_{13}ClN_2NaO_4$: 331.0462; found 331.0448.

4-Fluoro-2-(5-methylisoxazole-3-carboxamido)benzyl acetate (18e): The compound was



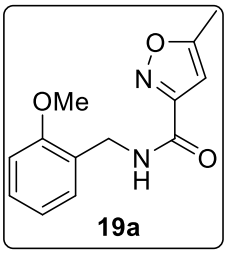
obtained after purification by column chromatography on silica gel (EtOAc:Hexanes = 20:80) as a colourless solid; Yield: 80% (46 mg); mp: 140-142 °C, R_f = 0.30. IR (DCM): 3377, 2917, 1707, 1610 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 9.73 (br s, 1H), 8.00 (dd, J_1 = 10.7 Hz, J_2 = 2.0 Hz, 1H), 7.36-7.32 (m, 1H), 6.88 (td, J_1 = 8.1 Hz, J_2 = 2.0 Hz, 1H), 6.54 (s, 1H), 5.13 (s, 2H), 2.52 (s, 3H), 2.16 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 171.8, 171.2, 163.1 (d, J = 245.0 Hz), 158.9, 157.3, 137.7 (d, J = 11.6 Hz), 132.3 (d, J = 9.7 Hz), 121.6 (d, J = 3.3 Hz), 112.0 (d, J = 21.7 Hz), 110.3 (d, J = 26.7 Hz), 101.5, 63.4, 20.8, 12.4; HRMS (ESI): *m/z* $[M + Na]^+$ calcd for $C_{14}H_{13}FN_2NaO_4$: 315.0757; found 315.0741.

5-Bromo-2-(5-methylisoxazole-3-carboxamido)benzyl acetate (18f): The compound was



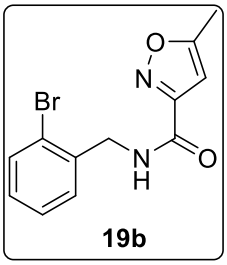
obtained after purification by column chromatography on silica gel (EtOAc:Hexanes = 20:80) as a colourless solid; Yield: 78% (54 mg); mp: 154-156 °C, R_f = 0.30. IR (DCM): 3370, 1702, 1608, 1584 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 9.60 (br s, 1H), 8.00 (d, J = 9.3 Hz, 1H), 7.53- 7.52 (m, 2H), 6.53 (s, 1H), 5.11 (s, 2H), 2.52 (s, 3H), 2.17 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 171.7, 171.1, 158.9, 157.3, 135.0, 133.5, 132.6, 128.5, 125.0, 118.1, 101.5, 63.2, 20.8, 12.4; HRMS (ESI): *m/z* $[M + Na]^+$ calcd for $C_{14}H_{13}BrN_2NaO_4$: 374.9956; found 374.9940.

***N*-(2-Methoxybenzyl)-5-methylisoxazole-3-carboxamide (19a):** The compound was



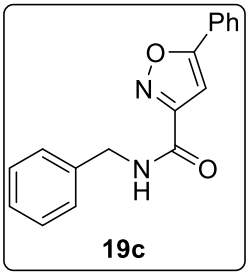
obtained after purification by column chromatography on silica gel (EtOAc:Hexanes = 20:80) as a colourless solid; Yield: 81% (200 mg, 1 mmol scale); mp: 80-82 °C, R_f = 0.40. IR (DCM): 2329, 1676, 1493, 1289 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.34-7.28 (m, 3H), 6.96-6.89 (m, 2H), 6.44 (s, 1H), 4.61 (d, J = 5.9 Hz, 2H), 3.89 (s, 3H), 2.47 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 171.0, 158.9, 158.8, 157.6, 129.8, 129.1, 125.5, 120.6, 110.3, 101.5, 55.4, 39.3, 12.3; HRMS (ESI): *m/z* $[M + Na]^+$ calcd for $C_{13}H_{14}N_2NaO_3$: 269.0902; found 269.0893.

***N*-(2-Bromobenzyl)-5-methylisoxazole-3-carboxamide (19b):** The compound was obtained after purification by column chromatography on silica gel (EtOAc:Hexanes = 20:80) as a colourless solid; Yield: 68% (200 mg, 1 mmol scale); mp: 96-98 ºC, R_f = 0.55. IR (DCM): 3324, 1676, 1542, 1457 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.58 (d, J = 7.9 Hz, 1H), 7.44 (d, J = 7.6 Hz, 1H), 7.32-7.29 (m, 2H), 7.18 (d, J = 7.7 Hz, 1H), 6.46 (s, 1H), 4.70 (d, J = 6.1 Hz, 2H), 2.48 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 171.3, 159.1, 158.5, 136.6, 132.9, 130.2, 129.4, 127.8, 123.7, 101.5, 43.7, 12.4; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{12}H_{12}BrN_2O_2$: 295.0082; found 295.0073.



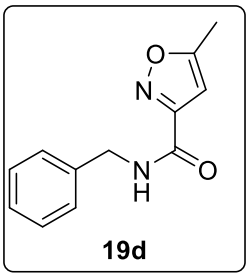
19b

***N*-(2-Methoxybenzyl)-5-phenylisoxazole-3-carboxamide (19c):** The compound was obtained after purification by column chromatography on silica gel (EtOAc:Hexanes = 20:80) as a colourless solid; Yield: 65% (200 mg, 0.2 mmol scale); mp: 150-152 ºC, R_f = 0.20. IR (DCM): 3315, 1673, 1491, 1242 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.81-7.79 (m, 2H), 7.50- 7.40 (m, 4H), 7.37 (d, J = 7.3 Hz, 1H), 7.33-7.28 (m, 1H), 6.99 (s, 1H), 6.98-6.91 (m, 2H), 4.67 (d, J = 6.0 Hz, 2H), 3.91 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 171.4, 159.3, 158.6, 157.7, 130.7, 129.9, 129.2, 129.1, 126.8, 125.9, 125.4, 120.7, 110.4, 99.3, 55.4, 39.4; HRMS (ESI): *m/z* $[M + Na]^+$ calcd for $C_{18}H_{16}N_2NaO_3$: 331.1059; found 331.1046.



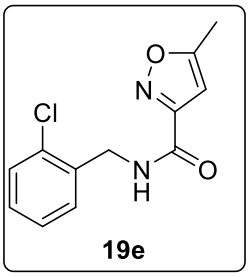
19c

***N*-Benzyl-5-methylisoxazole-3-carboxamide (19d):** The compound was obtained after purification by column chromatography on silica gel (EtOAc:Hexanes = 20:80) as a colourless solid; Yield: 77% (500 mg, 5 mmol scale); mp: 126-128 ºC, *Rf* = 0.50. IR (DCM): 3292, 1657, 1551, 1454 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.35-7.25 (m, 6H), 6.47 (s, 1H), 4.63 (d, J = 5.8 Hz, 2H), 2.48 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 171.2, 159.1, 158.7, 137.5, 128.8, 127.9, 127.7, 101.5, 43.4, 12.3; HRMS (ESI): *m/z* $[M + Na]^+$ calcd for $C_{12}H_{12}N_2NaO_2$: 239.0796; found 239.0784.

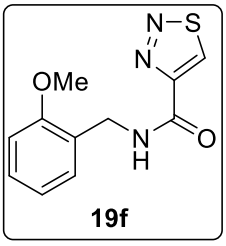


19d

***N*-(2-Chlorobenzyl)-5-methylisoxazole-3-carboxamide (19e):** The compound was obtained after purification by column chromatography on silica gel (EtOAc:Hexanes = 20:80) as a colourless solid; Yield: 72% (180 mg, 1 mmol scale); mp: 97-99 °C, R_f = 0.60. IR (DCM): 3342, 1676, 1543, 1457 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.44-7.38 (m, 2H), 7.32-7.25 (m, 2H), 6.46 (s, 1H), 4.71 (d, J = 6.0 Hz, 2H), 2.48 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 171.3, 159.1, 158.6, 134.9, 133.7, 130.1, 129.6, 129.1, 127.1, 101.5, 41.3, 12.3. HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{12}H_{12}ClN_2O_2$: 251.0587; found 251.0593.



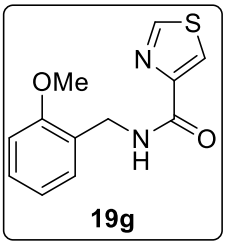
19e



19f

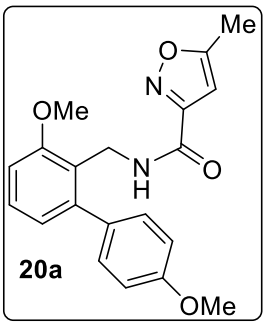
***N*-(2-Methoxybenzyl)-1,2,3-thiadiazole-4-carboxamide (19f):** The compound was obtained after purification by column chromatography on silica gel (EtOAc:Hexanes = 20:80) as a colourless solid; Yield: 74% (370 mg, 2 mmol scale), mp: 155-157 °C, R_f = 0.40, IR (DCM): 1677, 1538, 1493, 1244 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 9.24 (s, 1H), 8.12 (s, 1H), 7.37 (d, J = 7.4 Hz, 1H), 7.32-7.28 (m, 1H), 6.96-6.90 (m, 2H), 4.73 (d, J = 6.1 Hz, 2H), 3.91 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 158.5, 158.2, 157.7, 139.8, 129.9, 129.2, 125.5, 120.7, 110.4, 55.4, 39.6; HRMS (ESI): *m/z* $[M + Na]^+$ calcd for $C_{11}H_{11}N_3NaO_2S$: 272.0470; found 272.0466.

***N*-(2-Methoxybenzyl)thiazole-4-carboxamide (19g):** The compound was obtained after purification by column chromatography on silica gel (EtOAc:Hexanes = 20:80) as a colourless solid; Yield: 64% (160 mg, 1mmol scale), mp: 97-99 °C, R_f = 0.50, IR (DCM): 2926, 1658, 1546, 1491 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 8.71 (s, 1H), 8.16 (s, 1H), 7.90 (s, 1H), 7.34 (d, J = 7.4 Hz, 1H), 7.26 (t, J = 7.8 Hz, 1H), 6.94-6.87 (m, 2H), 4.65 (d, J = 6.1 Hz, 2H), 3.87 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 160.7, 157.6, 152.7, 151.3, 129.6, 128.9, 126.0, 123.1, 102.6, 110.3, 55.4, 39.1; HRMS (ESI): *m/z* $[M + Na]^+$ calcd for $C_{12}H_{12}N_2NaO_2S$: 271.0517; found 271.0528.



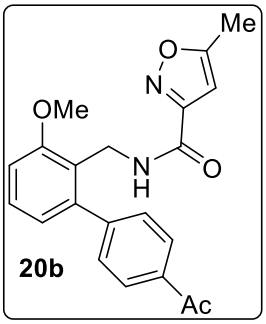
19g

***N*-((3,4'-Dimethoxy-[1,1'-biphenyl]-2-yl)methyl)-5-methylisoxazole-3-carboxamide**



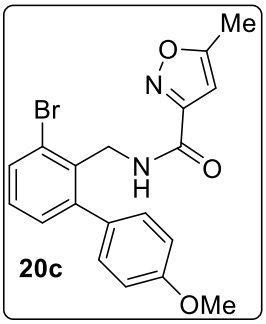
(20a): The compound was obtained after purification by column chromatography on silica gel (EtOAc:Hexanes = 20:80) as a yellow coloured solid; Yield: 88% (62 mg); mp: 126-128 ^{o}C, R_f = 0.20. IR (DCM): 3421, 1682, 1538, 1457 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.35-7.28 (m, 4H), 6.97 (d, J = 8.0 Hz, 2H), 6.92 (d, J = 8.0 Hz, 2H), 6.44 (s, 1H), 4.61 (d, J = 5.3 Hz, 2H), 3.94 (s, 3H), 3.86 (s, 3H), 2.46 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 170.9, 159.0, 159.0, 158.6, 158.4, 143.6, 132.7, 130.4, 128.6, 122.9, 122.9, 113.7, 109.2, 101.5, 55.8, 55.3, 36.9, 12.3; HRMS (ESI): *m/z* [M + Na]$^{+}$ calcd for $C_{20}H_{20}N_2NaO_4$: 375.1321; found 375.1306.

***N*-((4'-Acetyl-3-methoxy-[1,1'-biphenyl]-2-yl)methyl)-5-methylisoxazole-3-carboxamide**



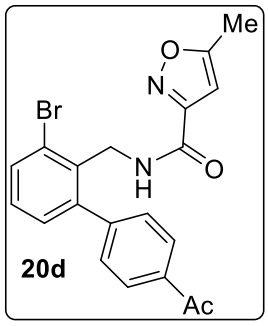
(20b): The compound was obtained after purification by column chromatography on silica gel (EtOAc:Hexanes = 20:80) as a yellow coloured solid; Yield: 83% (60 mg); mp: 143-145 ^{o}C, R_f = 0.15. IR (DCM): 1681, 1582, 1457, 1358 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.03 (d, J = 7.4 Hz, 2H), 7.45 (d, J = 7.4 Hz, 2H), 7.37 (t, J = 7.9 Hz, 1H), 7.28 (s, 1H), 6.98 (d, J = 8.2 Hz, 2H), 6.91 (d, J = 7.7 Hz, 1H), 6.41 (s, 1H), 4.55 (d, J = 5.2 Hz, 2H), 3.96 (s, 3H), 2.65 (s, 3H), 2.47 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 197.9, 171.0, 158.9, 158.6, 158.2, 145.3, 142.7, 136.0, 129.6, 128.9, 128.4, 122.8, 122.4, 110.1, 101.5, 55.8, 36.7, 26.7, 12.4; HRMS (ESI): *m/z* [M + Na]$^{+}$ calcd for $C_{21}H_{20}N_2NaO_4$: 387.1321; found 387.1312.

***N*-((3-Bromo-4'-methoxy-[1,1'-biphenyl]-2-yl)methyl)-5-methylisoxazole-3-carboxamide**



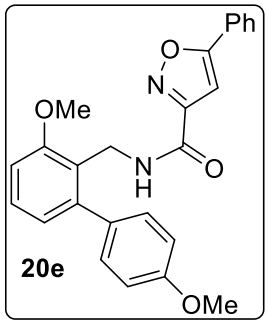
(20c): The compound was obtained after purification by column chromatography on silica gel (EtOAc:Hexanes = 20:80) as a colourless solid; Yield: 75% (60 mg); mp:106-108 ^{o}C, R_f = 0.30. IR (DCM): 1676, 1514, 1454, 1247 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.61 (d, J = 7.2 Hz, 1H), 7.26-7.20 (m, 4H), 6.97-6.95 (m, 3H), 6.43 (s, 1H), 4.66 (d, J = 4.8 Hz, 2H), 3.85 (s, 3H), 2.47 (s, 3H). 13C NMR (101 MHz, $CDCl_3$): δ 171.1, 159.2, 158.5, 158.3, 145.2, 133.7, 132.4, 132.2, 130.1, 130.0, 129.3, 126.1, 113.9, 101.4, 55.3, 41.9, 12.4. HRMS (ESI): *m/z* [M + Na]$^{+}$ calcd for $C_{19}H_{17}BrN_2NaO_3$: 423.0320; found 423.0313.

***N*-((4'-Acetyl-3-bromo-[1,1'-biphenyl]-2-yl)methyl)-5-methylisoxazole-3-carboxamide**



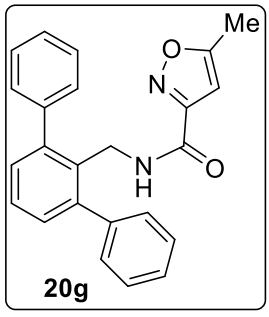
(20d): The compound was obtained after purification by column chromatography on silica gel (EtOAc:Hexanes = 20:80) as a colourless solid; Yield: 67% (55 mg); mp:154-156 ^{o}C, R_f = 0.25. IR (DCM): 1681, 1604, 1538, 1455 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.01 (d, J = 7.7 Hz, 2H), 7.66 (d, J = 7.2 Hz, 1H), 7.41 (d, J = 7.6 Hz, 2H), 7.27-7.23 (m, 2H), 7.01 (s, 1H), 6.40 (s, 1H), 4.62 (d, J = 5.1 Hz, 2H), 2.64 (s, 3H), 2.46 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 197.6, 171.2, 158.4, 158.3, 144.9, 144.2, 136.3, 133.5, 133.0, 129.5, 129.3, 128.5, 126.3, 101.4, 41.7, 26.7, 12.4. HRMS (ESI): *m/z* [M + Na]$^{+}$ calcd for $C_{20}H_{17}BrN_2NaO_3$: 435.0320; found 435.0332.

***N*-((3,4'-Dimethoxy-[1,1'-biphenyl]-2-yl)methyl)-5-phenylisoxazole-3-carboxamide**



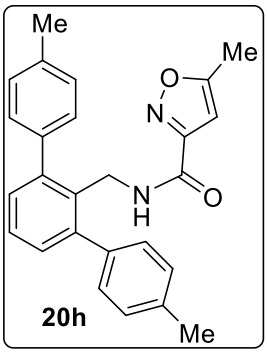
(20e): The compound was obtained after purification by column chromatography on silica gel (EtOAc:Hexanes = 30:70) as a colourless solid; Yield: 73% (60 mg); mp:133-135 ^{o}C, R_f = 0.20. IR (DCM):3419, 1610, 1446, 1174 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.81-7.80 (m, 2H), 7.50-7.49 (m, 3H), 7.37-7.28 (m, 4H), 7.01-6.94 (m, 5H), 4.65 (d, J = 5.4 Hz, 2H), 3.97 (s, 3H), 3.87 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 171.3, 159.4, 159.0, 158.6, 158.0, 143.6, 132.7, 130.6, 130.4, 129.1, 128.6, 126.9, 125.9, 123.0, 122.9, 113.8, 109.2, 99.3, 55.8, 55.3, 37.0; HRMS (ESI): *m/z* [M + Na]$^{+}$ calcd for $C_{25}H_{22}N_2NaO_4$: 437.1477; found 437.1495.

***N*-([1,1':3',1''-Terphenyl]-2'-ylmethyl)-5-methylisoxazole-3-carboxamide (20g):** The



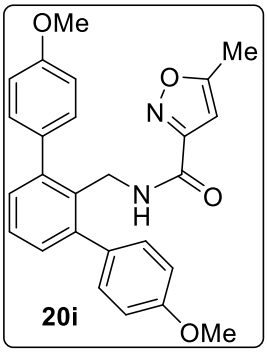
compound was obtained after purification by column chromatography on silica gel (EtOAc:Hexanes = 20:80) as a colourless solid; Yield: 90% (66 mg); mp: 150-152 ^{o}C, R_f = 0.60. IR (DCM): 2853, 1685, 1532, 760 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.43-7.36 (m, 11H), 7.34 (d, J = 7.5 Hz, 2H), 6.51 (s, 1H), 6.27 (s, 1H), 4.52 (d, J = 4.5 Hz, 2H), 2.44 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 170.8, 158.4, 157.6, 143.7, 140.9, 131.9, 129.8, 129.0, 128.4, 127.6, 127.4, 101.2, 39.1, 12.3; HRMS (ESI): *m/z* [M + Na]$^{+}$ calcd for $C_{24}H_{20}N_2NaO_2$: 391.1422; found 391.1410.

***N*-((4,4''-Dimethyl-[1,1':3',1''-terphenyl]-2'-yl)methyl)-5-methylisoxazole-3-**



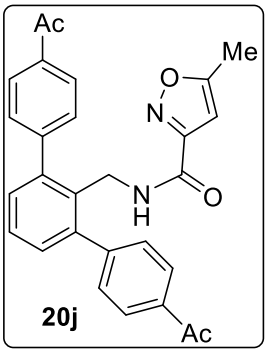
carboxamide (20h): The compound was obtained after purification by column chromatography on silica gel (EtOAc:Hexanes = 20:80) as a colourless solid; Yield: 90% (86 mg); mp:90-92 ^{o}C, R_f = 0.50. IR (DCM): 1685, 1534, 1457, 1422 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.44-7.40 (m, 1H), 7.32-7.29 (m, 6H), 7.25-7.23 (m, 4H), 6.55 (s, 1H), 6.30 (s, 1H), 4.52 (d, J = 5.0 Hz, 2H), 2.46 (s, 3H), 2.41 (s, 6H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 170.7, 158.5, 157.7, 143.7, 138.1, 137.0, 132.0, 129.8, 129.1, 128.9, 127.6, 101.2, 39.2, 21.2, 12.3. HRMS (ESI): *m/z* [M + Na]$^{+}$ calcd for $C_{26}H_{24}N_2NaO_2$: 419.1735; found 419.1719.

***N*-((4,4''-Dimethoxy-[1,1':3',1''-terphenyl]-2'-yl)methyl)-5-methylisoxazole-3-**



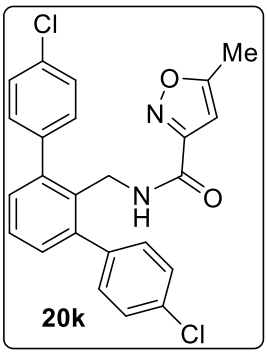
carboxamide (20i): The compound was obtained after purification by column chromatography on silica gel (EtOAc:Hexanes = 20:80) as a colourless solid; Yield: 82% (70 mg); mp:123-125 ^{o}C, R_f = 0.25. IR (DCM): 1682, 1513, 1457, 1246 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.40 (t, J = 7.6 Hz, 1H), 7.32-7.28 (m, 6H), 6.94 (d, J = 8.1 Hz, 4H), 6.52 (s, 1H), 6.29 (s, 1H), 4.52 (d, J = 4.7 Hz, 2H), 3.85 (s, 6H), 2.45 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 170.8, 158.9, 158.5, 157.7, 143.4, 133.4, 132.2, 130.1, 129.8, 127.6, 113.8, 101.2, 55.3, 39.3, 12.3; HRMS (ESI): *m/z* [M + Na]$^{+}$ calcd for $C_{26}H_{24}N_2NaO_4$: 451.1634; found
451.1616.

***N*-((4,4''-Diacetyl-[1,1':3',1''-terphenyl]-2'-yl)methyl)-5-methylisoxazole-3-carboxamide**



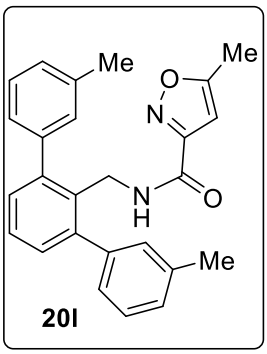
(20j): The compound was obtained after purification by column chromatography on silica gel (EtOAc:Hexanes = 20:80) as a colourless solid; Yield: 84% (76 mg); mp:126-128 ^{o}C, R_f = 0.25. IR (DCM): 3331, 1680, 1535, 1457 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.00 (d, J = 8.1 Hz, 4H), 7.49-7.48 (m, 5H), 7.31 (d, J = 7.6 Hz, 2H), 6.49 (s, 1H), 6.21 (s, 1H), 4.45 (d, J = 4.9 Hz, 2H), 2.63 (s, 6H), 2.43 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 197.6, 171.1, 158.1, 157.7, 145.6, 142.7, 136.1, 131.5, 130.0, 129.3, 128.5, 128.0, 101.1, 39.0, 26.7, 12.3; HRMS (ESI): *m/z* [M + Na]$^{+}$ calcd for $C_{28}H_{24}N_2NaO_4$: 475.1634; found 475.1618.

***N*-((4,4''-Dichloro-[1,1':3',1''-terphenyl]-2'-yl)methyl)-5-methylisoxazole-3-carboxamide**



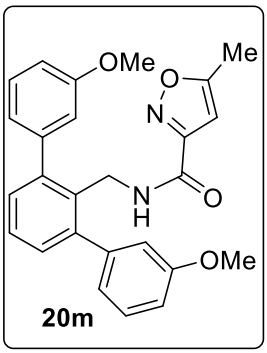
(20k): The compound was obtained after purification by column chromatography on silica gel (EtOAc:Hexanes = 20:80) as a colourless solid; Yield: 51% (44 mg); mp:117-119 ^{o}C, R_f = 0.55. IR (DCM): 3419, 1661, 1492, 1456 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.45-7.38 (m, 5H), 7.32-7.28 (m, 6H), 6.47 (s, 1H), 6.29 (s, 1H), 4.46 (d, J = 4.7 Hz, 2H), 2.46 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 171.0, 158.2, 157.7, 142.5, 139.2, 133.6, 131.8, 130.3, 130.1, 128.6, 127.9, 101.2, 39.0, 12.3; HRMS (ESI): *m/z* [M + Na]+ calcd for $C_{24}H_{18}Cl_2N_2NaO_2$:459.0643; found 459.0630.

***N*-((3,3''-Dimethyl-[1,1':3',1''-terphenyl]-2'-yl)methyl)-5-methylisoxazole-3-**



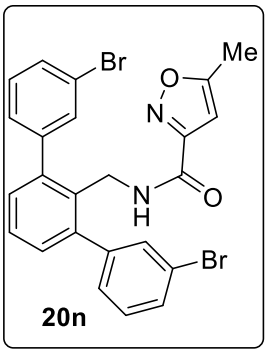
carboxamide (20l): The compound was obtained after purification by column chromatography on silica gel (EtOAc:Hexanes = 20:80) as a colourless solid; Yield: 57% (45 mg); mp:110-112 ^{o}C, R_f = 0.60. IR (DCM): 3332, 1785, 1482, 1236 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.42 (t, J = 7.5 Hz, 1H), 7.33-7.30 (m, 4H), 7.20-7.17 (m, 6H), 6.52 (s, 1H), 6.28 (s, 1H), 4.49 (d, J = 4.7 Hz, 2H), 2.45 (s, 3H), 2.37 (s, 6H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 170.8, 158.5, 157.6, 143.8, 140.9, 138.0, 131.9, 129.9, 129.6, 128.3, 128.1, 127.5, 126.0, 101.2, 39.1, 21.4, 12.3. HRMS (ESI): *m/z* [M + Na]$^{+}$ calcd for $C_{26}H_{24}N_2NaO_2$: 419.1735; found 419.1721.

***N*-((3,3''-Dimethoxy-[1,1':3',1''-terphenyl]-2'-yl)methyl)-5-methylisoxazole-3-**



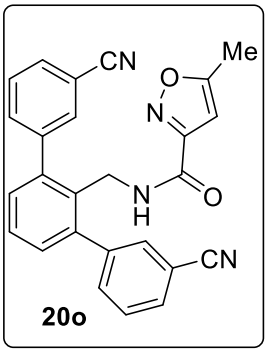
carboxamide (20m): The compound was obtained after purification by column chromatography on silica gel (EtOAc:Hexanes = 20:80) as a colourless solid; Yield: 82% (70 mg); mp:107-109 ^{o}C, R_f = 0.25. IR (DCM): 3432, 1687, 1592, 1231 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.43 (t, J = 7.5 Hz, 1H), 7.35-7.32 (m, 4H), 6.98 (d, J = 7.5 Hz, 2H), 6.93-6.91 (m, 4H), 6.54 (s, 1H), 6.28 (s, 1H), 4.52 (d, J = 4.7 Hz, 2H), 3.81 (s, 6H), 2.44 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 170.8, 159.4, 158.4, 157.7, 143.5, 142.2, 131.9, 129.7, 129.5, 127.6, 121.4, 114.3, 113.5, 101.2, 55.2, 39.1, 12.3; HRMS (ESI): *m/z* [M + Na]$^{+}$ calcd for $C_{26}H_{24}N_2NaO_4$: 451.1634; found 451.1624.

***N*-((3,3''-Dibromo-[1,1':3',1''-terphenyl]-2'-yl)methyl)-5-methylisoxazole-3-carboxamide**



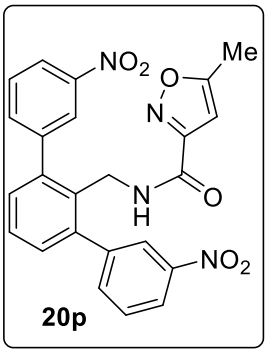
(20n): The compound was obtained after purification by column chromatography on silica gel (EtOAc:Hexanes = 20:80) as a colourless solid; Yield: 90% (90 mg); mp: 115-117 ^{o}C, R_f = 0.60. IR (DCM): 1683, 1595, 1557, 1455 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.52-7.49 (m, 4H), 7.43 (dd, J_1 = 7.8 Hz, J_2 = 7.4 Hz, 1H), 7.33-7.27 (m, 6H), 6.46 (s, 1H), 6.28 (s, 1H), 4.45 (d, J = 5.1 Hz, 2H), 2.46 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 171.0, 158.2, 157.7, 142.7, 142.2, 132.0, 131.9, 130.6, 130.1, 129.9, 127.8, 127.6, 122.5, 101.2, 38.8, 12.3. HRMS (ESI): *m/z* [M + H]$^{+}$ calcd for $C_{24}H_{19}Br_2N_2O_2$: 524.9813; found 524.9810.

***N*-((3,3''-Dicyano-[1,1':3',1''-terphenyl]-2'-yl)methyl)-5-methylisoxazole-3-carboxamide**



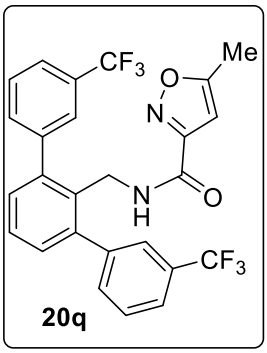
(20o): The compound was obtained after purification by column chromatography on silica gel (EtOAc:Hexanes = 20:80) as a colourless solid; Yield: 60% (50 mg); mp: 218-220 ^{o}C, R_f = 0.25. IR (DCM): 2229, 1676, 1606, 1537 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.72 (d, J = 8.2 Hz, 4H), 7.51-7.48 (m, 5H), 7.31 (d, J = 7.6 Hz, 2H), 6.42 (s, 1H), 6.26 (s, 1H), 4.42 (d, J = 5.1 Hz, 2H), 2.46 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 171.4, 157.9, 157.7, 145.3, 142.0, 132.3, 131.5, 130.3, 129.8, 128.3, 118.6, 111.6, 101.1, 38.7, 12.3. HRMS (ESI): *m/z* [M + Na]$^{+}$ calcd for $C_{26}H_{18}N_4NaO_2$: 441.1327; found 441.1307.

***N*-((3,3''-Dinitro-[1,1':3',1''-terphenyl]-2'-yl)methyl)-5-methylisoxazole-3-carboxamide**

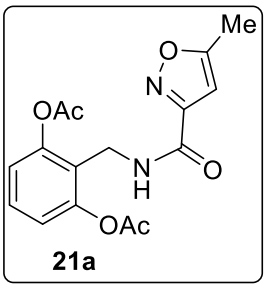


(20p): The compound was obtained after purification by column chromatography on silica gel (EtOAc:Hexanes = 20:80) as a yellow coloured solid; Yield: 66% (60 mg); mp: 178-180 ^{o}C, R_f = 0.20. IR (DCM): 1676, 1527, 1459, 1349 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.25-8.24 (m, 4H), 7.75 (d, J = 7.5 Hz, 2H), 7.65-7.61 (m, 2H), 7.52 (t, J = 7.7 Hz, 1H), 7.37 (d, J = 7.6 Hz, 2H), 6.51 (s, 1H), 6.20 (s, 1H), 4.42 (d, J = 4.9 Hz, 2H), 2.43 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 171.4, 157.9, 157.8, 148.1, 142.1, 141.5, 135.0, 132.1, 130.6, 129.6, 128.4, 124.0, 122.7, 101.0, 38.6, 12.3; HRMS (ESI): *m/z* [M + Na]$^{+}$ calcd for $C_{24}H_{18}N_4NaO_6$: 481.1124; found 481.1144.

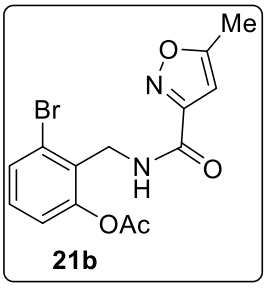
***N*-((3,3''-Bis(trifluoromethyl)-[1,1':3',1''-terphenyl]-2'-yl)methyl)-5-methylisoxazole-3-carboxamide (20q):** The compound was obtained after purification by column chromatography on silica gel (EtOAc:Hexanes = 20:80) as a colourless solid; Yield: 62% (62 mg); mp: 142-144 °C, R_f = 0.55. IR (DCM): 3436, 1643, 1458, 1426 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.64-7.54 (m, 8H), 7.49 (t, J =7.5 Hz, 1H), 7.34 (d, J = 7.6 Hz, 2H), 6.48 (s, 1H), 6.23 (s, 1H), 4.42 (d, J = 4.7 Hz, 2H), 2.44 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 171.1, 158.0, 157.6, 142.4, 141.4, 132.2, 132.0, 130.8 (q, J = 33.3 Hz), 130.3, 129.8, 128.1, 125.9 (q, J = 3.7 Hz), 124.4 (q, J = 3.6 Hz), 123.9 (q, J = 271.0 Hz), 101.0, 38.8, 12.2. HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{26}H_{19}F_6N_2O_2$: 505.1351; found 505.1366.



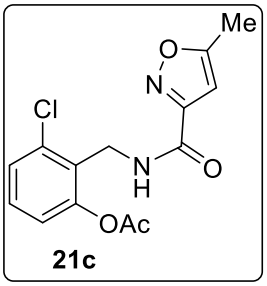
2-((5-Methylisoxazole-3-carboxamido)methyl)-1,3-phenylenediacetate (21a): The compound was obtained after purification by column chromatography on silica gel (EtOAc:Hexanes = 20:80) as a colourless solid; Yield: 70% (64 mg); mp: 112-114 °C, R_f = 0.20. IR (DCM): 1766, 1681, 1542, 1464 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.36 (t, J = 8.2 Hz, 1H), 7.03-7.01 (m, 3H), 6.40 (s, 1H), 4.51 (d, J = 5.6 Hz, 2H), 2.44 (s, 3H), 2.35 (s, 6H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 171.1, 169.5, 158.6, 158.4, 150.2, 129.3, 122.7, 120.4, 101.2, 32.8, 20.9, 12.3. HRMS (ESI): *m/z* $[M + Na]^+$ calcd for $C_{16}H_{16}N_2NaO_6$: 355.0906; found 355.0894.



3-Bromo-2-((5-methylisoxazole-3-carboxamido)methyl)phenylacetate (21b): The compound was obtained after purification by column chromatography on silica gel (EtOAc:Hexanes = 20:80) as a colourless solid; Yield: 77% (54 mg); mp: 126-128 °C, R_f = 0.20. IR (DCM): 3411, 2923, 1765, 1684 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.50 (d, J = 8.0 Hz, 1H), 7.22 (t, J = 8.1 Hz, 1H), 7.10-7.06 (m, 2H), 6.42 (s, 1H), 4.74 (d, J = 5.9 Hz, 1H), 2.45 (s, 3H), 2.38 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 171.2, 169.5, 158.6, 158.4, 150.2, 130.7, 130.0, 129.5, 125.7, 122.4, 101.4, 37.9, 20.9, 12.3. HRMS (ESI): *m/z* $[M + Na]^+$ calcd for $C_{14}H_{13}BrN_2NaO_4$: 374.9956; found 374.9943.



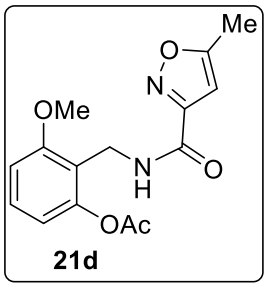
3-Chloro-2-((5-methylisoxazole-3-carboxamido)methyl)phenylacetate (21c): The



21c

compound was obtained after purification by column chromatography on silica gel (EtOAc:Hexanes = 20:80) as a colourless solid; Yield: 74% (45 mg); mp: 108-110 ^{o}C, R_f = 0.25. IR (DCM): 2923, 1680, 1452, 1008 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.35-7.31 (m, 2H), 7.05 (d, J = 6.6 Hz, 2H), 6.44 (s, 1H), 4.74 (d, J = 6.0 Hz, 2H), 2.48 (s, 3H), 2.41 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 171.2, 169.5, 158.7, 158.4, 150.2, 135.7, 129.6, 128.0, 127.4, 121.7, 101.4, 35.4, 20.9, 12.3. HRMS (ESI): *m/z* [M + Na]$^{+}$ calcd for $C_{14}H_{13}ClN_2NaO_4$: 331.0462; found 331.0477.

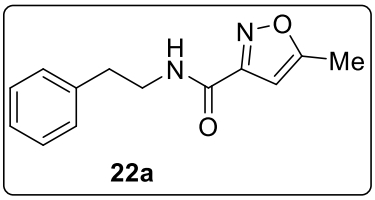
3-Methoxy-2-((5-methylisoxazole-3-carboxamido)methyl)phenylacetate (21d): The



21d

compound was obtained after purification by column chromatography on silica gel (EtOAc:Hexanes = 20:80) as a colourless solid; Yield: 72% (44 mg); mp: 113-115 ^{o}C, R_f = 0.20. IR (DCM): 1766, 1681, 1539, 1471 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.30 (t, J = 8.2 Hz, 1H), 7.13 (s, 1H), 6.81 (d, J = 8.3 Hz, 1H), 6.73 (d, J = 8.2 Hz, 1H), 6.42 (s, 1H), 4.61 (d, J = 5.8 Hz, 2H), 3.90 (s, 3H), 2.45 (s, 3H), 2.39 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 170.9, 169.7, 159.0, 158.8, 158.6, 149.7, 129.2, 118.2, 115.2, 108.2, 101.4, 55.9, 32.5, 20.9, 12.3. HRMS (ESI): *m/z* [M + Na]$^{+}$ calcd for $C_{15}H_{16}N_2NaO_5$: 327.0957; found 327.0971.

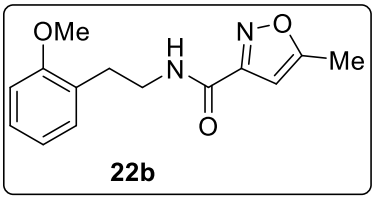
5-methyl-*N*-phenethylisoxazole-3-carboxamide (22a): The compound was obtained after



22a

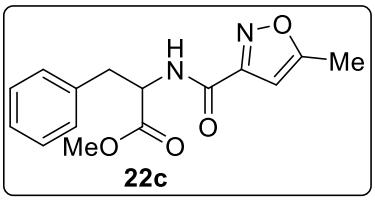
purification by column chromatography on silica gel (EtOAc:Hexanes = 20:80) as a colourless solid; Yield: 70% (805 mg, 5 mmol scale); mp: 92-94 ^{o}C, R_f = 0.40; IR (DCM): 3359, 1665, 1549, 1460 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.35-7.31 (m, 2H), 7.27-7.23 (m, 3H), 6.96 (br s, 1H), 6.45 (s, 1H), 3.70 (q, J = 6.6 Hz, 2H), 2.93 (t, J = 7.0 Hz, 2H), 2.48 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 171.1, 159.1, 158.8, 138.5, 128.7, 126.6, 101.4, 40.7, 35.7, 12.3. HRMS (ESI): *m/z* [M + H]$^{+}$ calcd for $C_{13}H_{15}N_2O_2$: 231.1134; found 231.1127.

***N*-(2-Methoxyphenethyl)-5-methylisoxazole-3-carboxamide (22b):** The compound was



22b

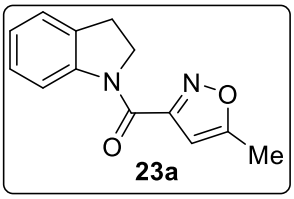
obtained after purification by column chromatography on silica gel (EtOAc:Hexanes = 20:80) as a colourless solid; Yield: 85% (440 mg, 2 mmol scale); mp:78-80 ^{o}C, R_f = 0.30. IR (DCM): 3342, 1699, 1549, 1494 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.28-7.22 (m, 2H), 7.17 (d, J = 7.3 Hz, 1H), 6.93-6.87 (m, 2H), 6.42 (s, 1H), 3.87 (s, 3H), 3.69-3.64 (m, 2H), 2.95 (t, J = 6.7 Hz, 2H), 2.46 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 170.9, 159.1, 158.9, 157.4, 130.6, 128.0, 127.2, 120.8, 110.3, 55.3, 40.2, 30.0, 12.3. HRMS (ESI): *m/z* $[M + Na]^+$ calcd for $C_{14}H_{16}N_2NaO_3$: 283.1059; found 283.1065.



22c

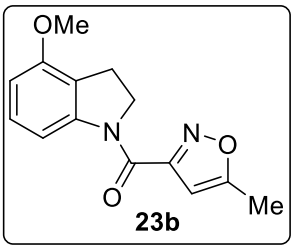
Methyl (5-methylisoxazole-3-carbonyl)phenylalaninate (22c): The compound was obtained after purification by column chromatography on silica gel (EtOAc:Hexanes = 20:80) as a colourless solid; Yield: 50% (288 mg, 2 mmol scale); mp: 86-88 ^{o}C, R_f = 0.40; IR (DCM): 1744, 1682, 1598, 1537 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.32 (d, J = 8.1 Hz, 2H), 7.28- 7.20 (m, 3H), 7.15 (d, J = 7.1 Hz, 2H), 6.39 (s, 1H), 5.02 (dd, J_1 = 14.1 Hz, J_2 = 6.2 Hz, 1H), 3.71 (s, 3H), 3.24 (dd, J_1 = 13.8 Hz, J_2 = 5.7 Hz, 1H), 3.17 (dd, J_1 = 13.9 Hz, J_2 = 6.5 Hz, 1H), 2.42 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 171.3, 171.2, 158.7, 158.2, 135.7, 129.2, 128.7, 127.2, 101.4, 53.3, 52.4, 37.9, 12.3. HRMS (ESI): *m/z* $[M + Na]^+$ calcd for $C_{15}H_{16}N_2NaO_4$: 311.1008; found 311.0998.

Indolin-1-yl(5-methylisoxazol-3-yl)methanone (23a): The compound was obtained after



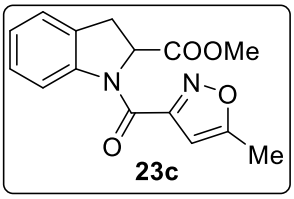
23a

purification by column chromatography on silica gel (EtOAc:Hexanes = 20:80) as a colourless solid; Yield: 56% (32 mg); mp: 95-97 ^{o}C, R_f = 0.60. IR (DCM): 3133, 1649, 1598, 1483 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.34 (d, J = 8.0 Hz, 1H), 7.29-7.25 (m, 2H), 7.12 (t, J = 7.5 Hz, 1H), 6.49 (s, 1H), 4.52 (t, J = 8.2 Hz, 2H), 3.23 (t, J = 8.2 Hz, 2H), 2.52 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 169.9, 160.3, 158.4, 142.7, 132.4, 127.5, 124.9, 124.8, 117.9, 103.2, 50.1, 28.4, 12.2. HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{13}H_{13}N_2O_2$: 229.0977; found 229.0970.



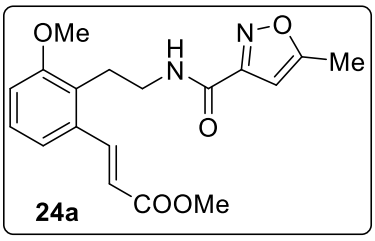
(4-Methoxyindolin-1-yl)(5-methylisoxazol-3-yl)methanone (23b): The compound was obtained after purification by column chromatography on silica gel (EtOAc:Hexanes = 20:80) as a colourless solid; Yield: 62% (32 mg); mp:148-150 ^{o}C, R_f = 0.60. IR (DCM): 2976, 1724, 1609, 1531 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.96 (d, J = 8.1 Hz, 1H), 7.25 (t, J = 8.2 Hz, 1H), 6.67 (d, J = 8.2 Hz, 1H), 6.47 (s, 1H), 4.52 (t, J = 8.4 Hz, 2H), 3.87 (s, 3H), 3.14 (t, J = 8.4 Hz, 2H), 2.51 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 169.8, 160.4, 158.4, 155.8, 144.0, 128.9, 119.8, 110.7, 107.1, 103.1, 55.4, 50.6, 25.5, 12.1. HRMS (ESI): *m/z* [M + Na]$^{+}$ calcd for $C_{14}H_{14}N_2NaO_3$: 281.0902; found 281.0913.

Methyl 1-(5-methylisoxazole-3-carbonyl)indoline-2-carboxylate (23c): The compound



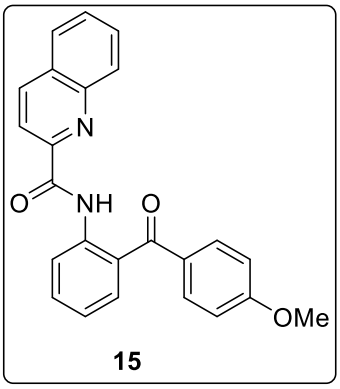
was obtained after purification by column chromatography on silica gel (EtOAc:Hexanes = 20:80) as a colourless solid; Yield: 50% (25 mg); mp:110-112 ^{o}C, R_f = 0.60. IR (DCM): 1749, 1651, 1482, 1274 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.40 (d, J = 8.1 Hz, 1H), 7.32-7.28 (m, 1H), 7.23 (d, J = 7.3 Hz, 1H), 7.13 (t, J = 7.4 Hz, 1H), 6.53 (s, 1H), 5.90 (dd, J_1 = 11.0 Hz, J_2 = 2.3 Hz, 1H), 3.71 (s, 3H), 3.70-3.65 (m, 1H), 3.35 (dd, J_1 = 16.5 Hz, J_2 = 1.5 Hz, 1H), 2.50 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 172.1, 169.9, 160.2, 158.7, 142.6, 129.3, 128.0, 125.1, 124.5, 117.9, 103.5, 61.8, 52.8, 33.6, 12.1. HRMS (ESI): *m/z* [M + Na]$^{+}$ calcd for $C_{15}H_{14}N_2NaO_4$: 309.0851; found 309.0866.

Methyl(*E*)-3-(3-methoxy-2-(2-(4-methylisoxazole-5-carboxamido)ethyl)phenyl)acrylate



(24a): The compound was obtained after purification by column chromatography on silica gel (EtOAc:Hexanes = 20:80) as a colourless solid; Yield: 88% (60 mg); mp; 154-156 ^{o}C, R_f = 0.20. IR (DCM): 3322, 1716, 1677, 1546 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.02 (d, J = 15.7 Hz, 1H), 7.29-7.23 (m, 1H), 7.18 (d, J = 7.5 Hz, 2H), 6.92 (d, J = 8.0 Hz, 1H), 6.40 (s, 1H), 6.34 (d, J = 15.7 Hz, 1H), 3.89 (s, 3H), 3.81 (s, 3H), 3.63-3.58 (m, 2H), 3.15 (t, J = 6.4 Hz, 2H), 2.46 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 170.9, 167.1, 159.2, 158.8, 157.7, 141.8, 135.0, 127.9, 127.0, 120.7, 119.2, 111.5, 101.3, 55.7, 51.8, 40.1, 24.8, 12.3. HRMS (ESI): *m/z* [M + Na]$^{+}$ calcd for $C_{18}H_{20}N_2NaO_5$: 367.1270; found 367.1252.

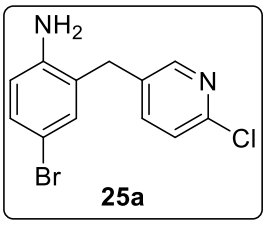
***N*-(2-(4-methoxybenzoyl)phenyl)quinoline-2-carboxamide (15):** The compound was



15

obtained after purification by column chromatography on silica gel (EtOAc:Hexanes = 20:80) as a colourless solid; Yield: 81% (92 mg); mp:138-140 ^{o}C, R_f = 0.40. IR (DCM): 3275, 2961, 1749, 1634 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 12.66 (br s, 1H), 8.88 (d, J = 8.2 Hz, 1H), 8.40-8.35 (m, 3H), 7.91-7.87 (m, 3H), 7.83-7.79 (m, 1H), 7.67-7.62 (m, 3H), 7.20 (td, J_1 = 7.8 Hz, J_2 = 1.0 Hz, 1H), 7.00-6.98 (m, 2H), 3.89 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 196.9, 163.5, 163.3, 149.8, 146.5, 139.0, 137.6, 133.1, 132.7, 132.5, 131.2, 130.5, 130.1, 129.4, 128.2, 127.5, 126.1, 122.5, 121.7, 118.8, 113.6, 55.5; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{24}H_{19}N_2O_3$: 383.1396; found 383.1382.

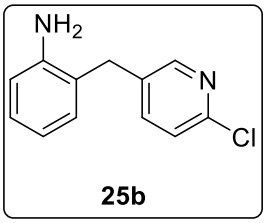
4-Bromo-2-((6-chloropyridin-3-yl)methyl)aniline (25a): The compound was obtained after



25a

purification by column chromatography on silica gel (EtOAc:Hexanes = 20:80) as a red coloured solid; Yield: 50% (25 mg); mp:112-114 ^{o}C, R_f = 0.30; IR (DCM): 3356, 2921, 1627, 1488 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.30 (dd, J_1 = 2.5 Hz, J_2 = 0.64 Hz, 1H), 7.43 (dd, J_1 = 8.2 Hz, J_2 = 2.5 Hz, 1H), 7.29-7.27 (m, 2H), 7.23 (dd, J_1 = 8.4 Hz, J_2 = 2.3 Hz, 1H), 7.12 (d, J = 2.3 Hz, 1H), 6.61 (d, J = 8.4 Hz, 1H), 3.83 (s, 2H), 3.55 (s, 2H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 150.0, 149.6, 143.4, 138.9, 133.0, 133.0, 131.0, 125.1, 124.4, 117.7, 110.7, 33.9. HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{12}H_{11}BrClN_2$: 296.9794; found 296.9780.

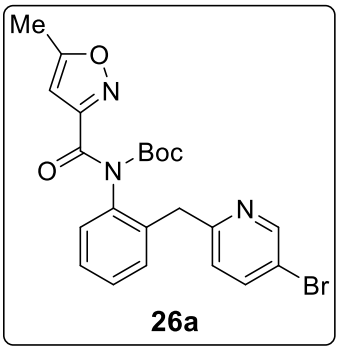
2-((6-Chloropyridin-3-yl)methyl)aniline (25b): The compound was obtained after



25b

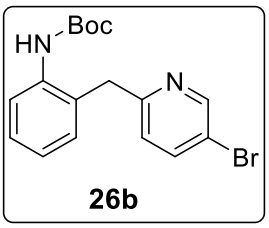
purification by column chromatography on silica gel (EtOAc:Hexanes = 20:80) as a yellow coloured solid; Yield: 35% (45 mg, 0.4 mmol scale); mp: 100-102 ^{o}C, R_f = 0.30; IR (DCM): 3342, 2856, 1581, 1085 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.31 (s, 1H), 7.44 (d, J = 8.1 Hz, 1H), 7.26 (d, J = 8.2 Hz, 1H), 7.15 (t, J = 7.6 Hz, 1H), 7.01 (d, J = 7.4 Hz, 1H), 6.80 (t, J = 7.5 Hz, 1H), 6.73 (d, J = 7.9 Hz, 1H), 3.88 (s, 2H), 3.54 (s, 2H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 149.7, 149.6, 144.3, 139.0, 133.9, 130.6, 128.3, 124.3, 123.2, 119.6, 116.2, 34.1; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{12}H_{12}ClN_2$: 219.0689; found 219.0694.

***Tert*-butyl(2-((5-bromopyridin-2-yl)methyl)phenyl)(5-methylisoxazole-3-carbonyl)carbamate (26a):** The compound was obtained after purification by column chromatography on silica gel (EtOAc:Hexanes = 20:80) as a yellow coloured liquid; Yield: 77% (50 mg); R_f = 0.40. IR (DCM): 1747, 1466, 1598, 1296 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 8.59 (s, 1H), 7.67 (d, J = 8.3 Hz, 1H), 7.36-7.35(m, 3H), 7.27 (d, J = 6.7 Hz, 1H), 7.10 (d, J = 8.4 Hz, 1H), 6.32 (s, 1H), 4.13 (s, 2H), 2.51 (s, 3H), 1.28 (s, 9H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 1710.1, 163.5, 159.8, 158.4, 152.1, 150.0, 139.0, 137.2, 136.4, 131.2, 129.3, 129.1, 127.9, 125.2, 118.4, 101.4, 84.5, 39.1, 27.5, 12.3. HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{22}H_{23}BrN_3O_4$: 472.0872; found 472.0853.



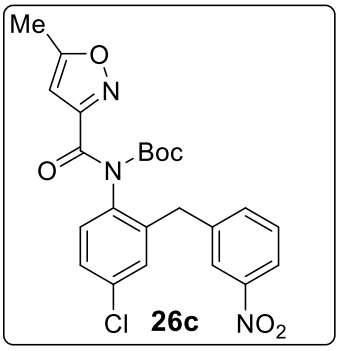
26a

***Tert*-butyl (2-((5-bromopyridin-2-yl)methyl)phenyl)carbamate (26b):** The compound was obtained after purification by column chromatography on silica gel (EtOAc:Hexanes = 20:80) as a yellow coloured liquid; Yield: 65% (28 mg); mp:100-102 ^oC, R_f = 0.35. IR (DCM): 2976, 1724, 1591, 1450 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 9.07 (s, 1H), 8.59 (s, 1H), 7.85 (d, J = 7.0 Hz, 1H), 7.75 (d, J = 8.2 Hz, 1H), 7.26-7.21(m, 2H), 7.15 (d, J = 8.2 Hz, 1H), 7.02 (t, J = 7.4 Hz, 1H), 4.05 (s, 2H), 1.59 (s, 9H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 159.2, 153.7, 149.9, 139.9, 137.5, 129.8, 129.3, 127.8, 124.2, 123.6, 122.7, 118.5, 79.9, 41.1, 28.4. HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{17}H_{20}BrN_2O_2$: 363.0708; found 363.0695.



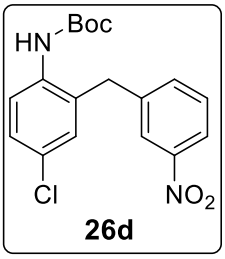
26b

***Tert*-butyl(4-chloro-2-(3-nitrobenzyl)phenyl)(5-methylisoxazole-3-carbonyl)carbamate (26c):** The compound was obtained after purification by column chromatography on silica gel (EtOAc:Hexanes = 20:80) as a light red coloured solid; Yield: 65% (306 mg); mp:138-140 ^oC, R_f = 0.60. IR (DCM): 1748, 1695, 1598, 1457 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 8.12-8.09 (m, 1H), 7.56 (d, J = 7.6 Hz, 1H), 7.48 (t, J = 7.8 Hz, 1H), 7.35 (d, J = 8.4 Hz, 1H), 7.22 (d, J = 8.4 Hz, 1H), 7.16 (s, 1H), 6.29 (s, 1H), 4.10, 4.03 (ABq, J = 15.8 Hz, 2H), 2.52 (s, 3H), 1.31 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 170.6, 163.4, 159.4, 151.8, 148.3, 140.7, 139.7, 135.6, 135.2, 135.0, 130.8, 130.6, 129.5, 128.3, 124.2, 121.8, 101.4, 85.1, 36.5, 27.5, 12.3. HRMS (ESI): *m/z* $[M + Na]^+$ calcd for $C_{23}H_{22}ClN_3NaO_6$: 494.1095; found 494.1076.



26c

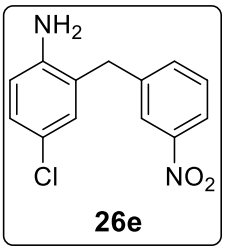
***Tert*-butyl (4-chloro-2-(3-nitrobenzyl)phenyl)carbamate (26d):** The compound was



26d

obtained after purification by column chromatography on silica gel (EtOAc:Hexanes = 20:80) as light red coloured solid; Yield: 70% (108 mg); mp: 148-150 ^{o}C R_f = 0.50. IR (DCM): 3333, 1684, 1531, 1347 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.12 (d, J = 7.6 Hz, 1H), 8.06 (br. s, 1H), 7.62 (d, J = 8.1 Hz, 1H), 7.51-7.47 (m, 2H), 7.26 (d, J = 8.7 Hz, 1H), 7.10 (s, 1H), 6.14 (s, 1H), 4.05 (s, 2H), 1.47 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 153.1, 148.5, 140.7, 134.8, 134.6, 132.6, 130.2, 130.1, 129.8, 127.9, 125.3, 123.5, 121.9, 81.0, 37.2, 28.2. HRMS (ESI): *m/z* [M - H]$^{+}$ calcd for $C_{18}H_{18}ClN_2O_4$: 361.0955; found 361.0942.

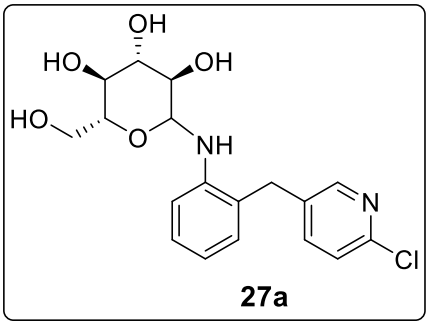
4-Chloro-2-(3-nitrobenzyl)aniline (26e): The compound was obtained after purification by



26e

column chromatography on silica gel (EtOAc:Hexanes = 20:80) as a yellow coloured solid; Yield: 90% (66 mg); mp:90-92 ^{o}C, R_f = 0.20. IR (DCM): 2953, 1479, 1651, 1482 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.10 (d, J = 7.7 Hz, 1H), 8.06 (s, 1H), 7.53-7.47 (m, 2H), 7.10 (d, J = 8.4 Hz, 1H), 7.10 (s, 1H), 6.66 (d, J = 8.4 Hz, 1H), 3.95 (s, 2H), 3.54 (s, 2H). ^{13}C NMR (101 MHz, CDCl3): δ 148.5, 143.1, 140.8, 134.7, 130.3, 129.7, 128.1, 124.9, 123.4, 123.4, 121.9, 117.3, 37.1. HRMS (ESI): *m/z* [M + H]$^{+}$ calcd for $C_{13}H_{12}ClN_2O_2$: 263.0587; found 263.0571.

(*3R,4S,5S,6R*)-2-((2-((6-chloropyridin-3-yl)methyl)phenyl)amino)-6-

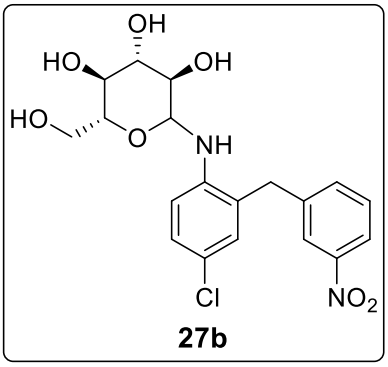


27a

(hydroxymethyl)tetrahydro-2*H*-pyran-3,4,5-triol (27a): The compound was obtained after purification by column chromatography on silica gel (MeOH:DCM = 10:90) as a brown coloured solid; Yield: 30% (23 mg); (*dr* 88:12), mp:159-161 ^{o}C, R_f = 0.30. IR (MeOH): 3436, 1638, 1456, 1081 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d^6): δ 8.33 (d, J = 2.3 Hz, 1H), 7.70 (dd, J_1 = 8.2 Hz, J_2 = 2.4 Hz,1H), 7.41 (d, J = 8.2 Hz, 1H), 7.10-7.05 (m, 1H), 6.94 (d, J = 7.5 Hz, 1H), 6.78 (d, J = 8.1 Hz, 1H), 6.66 (t, J = 7.3 Hz, 1H), 5.50 (d, J = 3.5 Hz, 1H), 5.03 (d, J = 3.5 Hz, 1H), 4.96-4.95 (m, 2H), 4.49 (t, J = 5.7 Hz, 1H), 4.30 (t, J = 7.2 Hz, 1H), 3.98 (d, J = 15.7 Hz, 1H), 3.87 (d, J = 15.7 Hz, 1H), 3.70-3.66 (m, 1H), 3.45 (q, J = 5.9 Hz, 1H), 3.28-3.22 (m, 3H), 3.16-3.13 (m, 1H). ^{13}C NMR (101 MHz, DMSO-d^6): δ 150.4, 148.4, 145.0, 140.6, 136.0, 130.1, 128.0, 124.9, 124.4, 118.3, 113.2, 86.2, 77.9,

77.9, 73.2, 70.7, 61.4, 32.8. HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{18}H_{22}ClN_2O_5$: 381.1217; found 381.1201. (NMR values corresponds to the major isomer).

(*3R,4S,5S,6R*)-2-((4-Chloro-2-(3-nitrobenzyl)phenyl)amino)-6-(hydroxymethyl)tetrahydro-2*H*-pyran-3,4,5-triol (27b): The compound was obtained after purification by column chromatography on silica gel (MeOH:DCM = 10:90) as a brown coloured solid; Yield: 46% (35 mg); (*dr* 80:20), mp: 170-172 °C, R_f = 0.20. IR (MeOH); 3435, 2066, 1637, 727 cm^{-1}; ^1H NMR (400 MHz, DMSO-d^6): δ 8.14 (s, 1H), 8.07 (d, *J* = 8.0 Hz, 1H), 7.73 (d, *J* = 7.6 Hz, 1H), 7.59 (t, *J* = 7.8 Hz, 1H), 7.11 (d, *J* = 8.6 Hz, 1H), 7.04 (s, 1H), 6.78 (d, *J* = 8.7 Hz, 1H), 5.69 (d, *J* = 6.5 Hz, 1H), 5.04-4.97 (m, 2H), 4.49 (t, *J* = 5.4 Hz, 1H), 4.29-4.25 (m, 1H), 4.15-4.03 (m, 2H), 3.69-3.65 (m, 1H), 3.46-3.42 (m, 2H), 3.30-3.13 (m, 4H); ^{13}C NMR (101 MHz, DMSO-d^6): δ 148.3, 144.1, 142.4, 136.2, 130.3, 129.7, 127.6, 127.2, 123.8, 121.7, 121.6, 114.8, 86.1, 77.9, 77.8, 73.0, 70.6, 61.4, 35.5. HRMS (ESI): *m/z* $[M + Na]^+$ calcd for $C_{19}H_{21}ClN_2NaO_7$: 447.0935; found 447.0954. (NMR values corresponds to the major isomer).



27b

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[13] It may be noted that, though the γ-C(sp^3)-H arylation products **12** were obtained in low to satisfactory yields. However, the MICA-aided γ-C(sp^3)-H acetoxylation of **11** and γ-C(sp^2)-H arylation/acetoxylation of **19** have effectively afforded the corresponding products in good yields (Schemes 5-9). Hence, the efficiency of MICA

as a DG in these reactions are comparable to picolinamide-aided reactions reported in the literature.