Studies on the Ni-Catalyzed Synthesis of Tertiary Amides and Pd-Catalyzed Synthesis of α-Naphthol-Based Triarylmethanes, *Ortho*-Arylated D-(-)-Phenylglycine Methyl Esters and *β*-Arylated Keto Acids

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

by

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Aug-2018

Dedicated to My Parents,

Brothers and Sister

Declaration

I hereby declare that the matter embodied in this thesis entitled "Studies on the Ni-Catalyzed Synthesis of Tertiary Amides and Pd-Catalyzed Synthesis of α-Naphthol-Based Triarylmethanes, *Ortho*-Arylated D-(-)-Phenylglycine Methyl Esters and *β*-Arylated Keto Acids" is the result of investigations carried out by me under the supervision of **Dr. S. Arulananda Babu** at the Department of Chemical Sciences, Indian Institute of Science Education and Research (IISER) Mohali, SAS Nagar Mohali, India. This work has not been submitted in part of full for the award of any degree, a diploma or a fellowship to any other university or institute. Whenever contributions of others are involved, every effort is made to indicate it clearly with due acknowledgements. In keeping with the general practice in reporting scientific observations, acknowledgements have been made whenever the work was described based on the findings of other investigators. Any omission that might have occurred due to oversight or error in judgement is regretted. A complete bibliography of the books and journals referred to is given at the end of the thesis.

Rathinam Sankar

Date:

Place:

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

Dr. S. Arulananda Babu

Associate Professor

Department of Chemical Sciences

Indian Institute of Science Education and Research Mohali

Date:

Place:

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It is my privilege to express my sincere thanks to my supervisor ***Dr. S. Arulananda Babu*** *for constant support throughout the work.*

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List of publications from the thesis work

1) **Sankar, R.;** Babu, S. A.* *Asian J. Org. Chem.* **2017**, *6*, 269.

Title: Construction of tertiary amides: Ni(II)-catalyzed *N*-arylation of secondary acyclic amides (2-picolinamides) with aryl halides.

2) **Sankar, R.;** Babu, S. A.* *Manuscript under preparation*

Title: Palladium-catalyzed desulfitative Heck reaction and synthesis of α-naphthol-based triarylmethanes.

3) **Sankar, R.;** Babu, S. A.* *Manuscript under preparation*

Title: Palladium-catalyzed *ortho*-arylation of D-(-)-2-phenylglycine methyl ester using bidentate picolinamide directing group.

4) **Sankar, R.;** Babu, S. A.* *Manuscript under preparation*

Title: Palladium-catalyzed bidentate ligand directed β-C(sp^3)-H functionalization on ε-, ζ-, η-keto acids.

List of Publication as a co-author

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

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

Conferences/Symposia

Presented poster entitled “Nickel catalyzed *N*-arylation of various *N*-alkylpicolinamides with aryl halides as coupling partner” **Rathinam Sankar**, S. Arulananda Babu at XII J-NOST Conference for Research Scholars CSIR-CDRI, Lucknow, India. (24 – 27) November, 2016.

Preamble

A literature survey revealed that the *N*-arylation and C-N bond formations have been well studied using Cu or Pd catalysts. Notably, the *N*-arylation and C-N bond formations have not been reported using Ni catalysts and a part of this thesis deals on the usage of nickel catalyst for the synthesis of tertiary amides via *N*-arylation and C-N bond formation. Next, the C-C bond formation by Heck coupling reactions has significantly attracted the attention of chemists. Aryl sulphonyl chlorides have also been introduced in the place of aryl halides for performing the Heck reactions. In this line, a part of this thesis work deals on synthesis of α-naphthol-based triarylmethanes via Heck coupling reaction. In recent years, the transition metal-catalyzed directed C-H functionalization reactions have emerged as one of the important synthetic organic transformations. In this line, a part of this thesis deals on the Pd-catalyzed bis-arylation of *ortho* C(sp^2)-H bonds of D-(-)-phenylglycine methyl esters and also β-C(sp^3)-H arylation of ε-, ζ-, η-keto acids.

This thesis entitled "Studies on the Ni-Catalyzed Synthesis of Tertiary Amides and Pd-Catalyzed Synthesis of α-Naphthol-Based Triarylmethanes, *Ortho*-Arylated D-(-)-Phenylglycine Methyl Esters and *β*-Arylated Keto Acids.

Chapter 1: Construction of tertiary amides: Ni(II)-catalyzed *N*-arylation of secondary acyclic amides (2-picolinamides) with aryl halides.

Chapter 2: Palladium-catalyzed desulfitative Heck reaction and synthesis of α-naphthol-based triarylmethanes.

Chapter 3: Palladium-catalyzed *ortho*-arylation of D-(-)-2-phenylglycine methyl ester using bidentate picolinamide directing group.

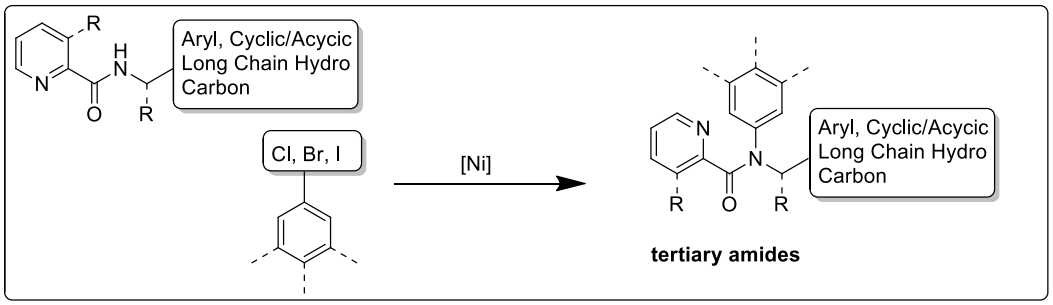
Chapter 4: Palladium-catalyzed bidentate ligand directed β-C(sp^3)-H functionalization on ε-, ζ-, η-keto acids.

Objectives

The research work carried out is focused on the utilization of Nickel(II) and Palladium(II) catalysts for the discovery of new methodologies toward the synthesis of tertiary amides, α-naphthol-based triarylmethanes, *ortho*-arylated D-(-)-phenylglycine methyl esters and *β*-arylated keto acids.

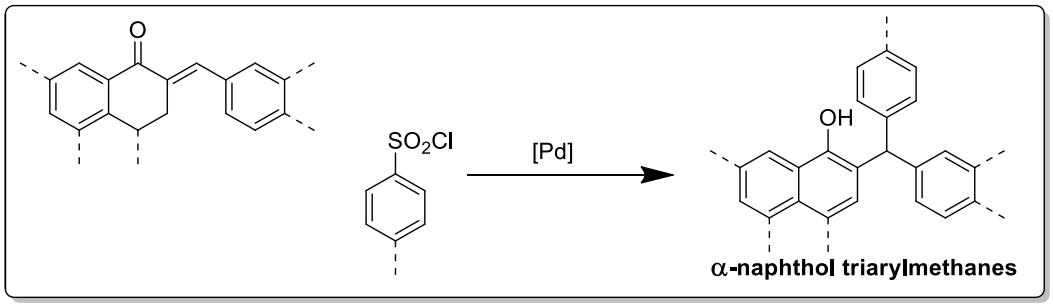
Objectives 1 (Chapter 1)

In particular, various tertiary amides are used as kinase inhibitor, anticoagulant, anticancer agents and antagonists. While the *N*-arylation and C-N bond formations have been well studied using Cu or Pd catalysts; the *N*-arylation of secondary amides and C-N bond formations have not been reported using Ni catalysts and a part of this thesis envisages the usage of nickel catalyst for the synthesis of tertiary amides via *N*-arylation of secondary amides and C-N bond formation.



Objectives 2 (Chapter 2)

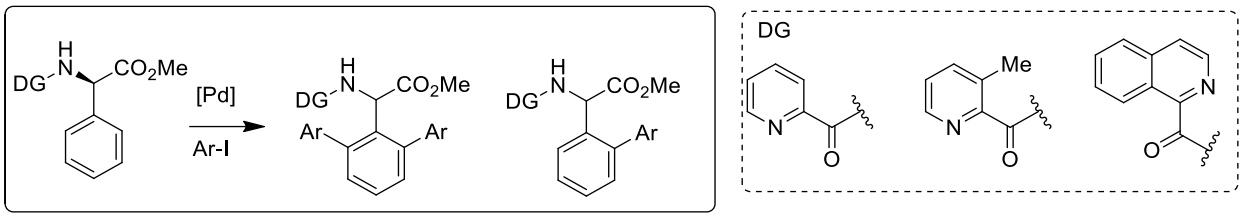
Triarylmethane molecules have found significant applications in medicinal chemistry, natural product synthesis, material science and as protecting group in peptide synthesis. In particular, α-naphthol-based triarylmethanes are utilized as anticancer agents and HIV-1 integrase antagonists. A part of this thesis work envisaged the synthesis of α-naphthol-based triarylmethanes via Heck coupling reaction.



Objectives (Chapter 3)

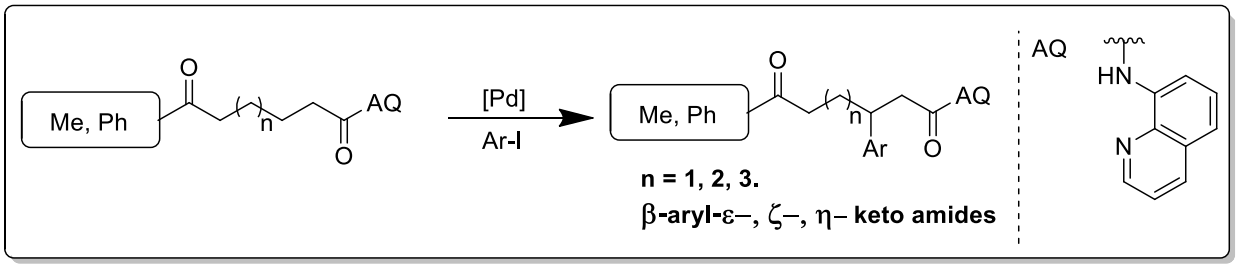
Natural and unnatural amino acids play an important role in peptidomimetics, glycopeptide synthesis, protein engineering and drug discovery. In particular phenylglycine amino acid

derivatives have found significant applications in medicinal chemistry (as aggregation, neurokinin and protease inhibitors, neurotransmitter and anticancer agents). A part of this thesis envisaged the synthesis of o*rtho*-arylated D-(-)-phenylglycine methyl esters via the Pd-catalyzed bis-arylation of *ortho* C(sp^2)-H bonds of D-(-)-phenylglycine methyl esters.



Objective 4 (Chapter 4)

Keto acids are an important class of building blocks and found various applications in the synthesis of various natural products, biologically active molecules. A part of this thesis envisaged on the synthesis of various *β*-arylated keto acids via the Pd-catalyzed β-C(sp^3)-H arylation of ε-, ζ-, η-keto acids.



Chapter 1: Construction of tertiary amides: Ni(II)-catalyzed *N*-arylation of secondary acyclic amides (2-picolinamides) with aryl halides.

Introduction

Nitrogen containing molecules have widespread applications in pharmaceuticals, organic materials, dyes and catalysis.[1] The C-N coupling reactions are attractive route to synthesize nitrogen containing heterocycles, natural products, synthesis of ligands, bioactive compounds and materials.[2] *N*-Arylation of amines/amides reaction via aromatic nucleophilic substitution[3] and transition metal catalyzed coupling process are important route to assemble *N*-arylated nitrogen containing compounds (Figures 1 and 2). The decreased nucleophilicity of amides makes them challenging substrates for the transition metal-catalyzed *N*-arylation/alkylation. Although many synthetic routes involving transition metal catalyzed *N*-arylation of primary amides[4] have been reported but limited reports are available for the *N*-arylation of secondary amides.[5a-c] In general, secondary amide *N*-arylation is a challenging reaction when compared to the *N*-arylation of primary amides. This is due to reduced nucleophilicity and steric hindrance provided by the second alkyl/aryl group on nitrogen atom that diminishes efficiency for coordination to the metal center and subsequently which slows down deprotonation step. A part of this thesis envisages the usage of nickel catalyst for the synthesis of tertiary amides via *N*-arylation of secondary amides and C-N bond formation.

Transition metals such as palladium[6a] and copper[6b] catalyzed *N*-arylations of primary and secondary amides have been studied extensively.[6-8] On the other hand, *N*-arylations of amides have not been well explored using inexpensive transition metal catalysts such as nickel and iron. There are various synthetic methods have been discovered for *N*-arylation and C-N bond formation (Scheme 1). The classical amination methods such as nitration followed by reduction and nuclophilic aromatic substitution reactions were found to have more drawbacks than the transition metal-catalyzed amination methods. In 1903, Fritz Ullmann introduced the transition metal promoted *N*-arylation reactions (Scheme 2A),[9a] Mixing of aniline derivative **1c** with *ortho*-chlorobenzoic acid **2d** in presence of metallic copper afforded the corresponding diarylamines **3e**.

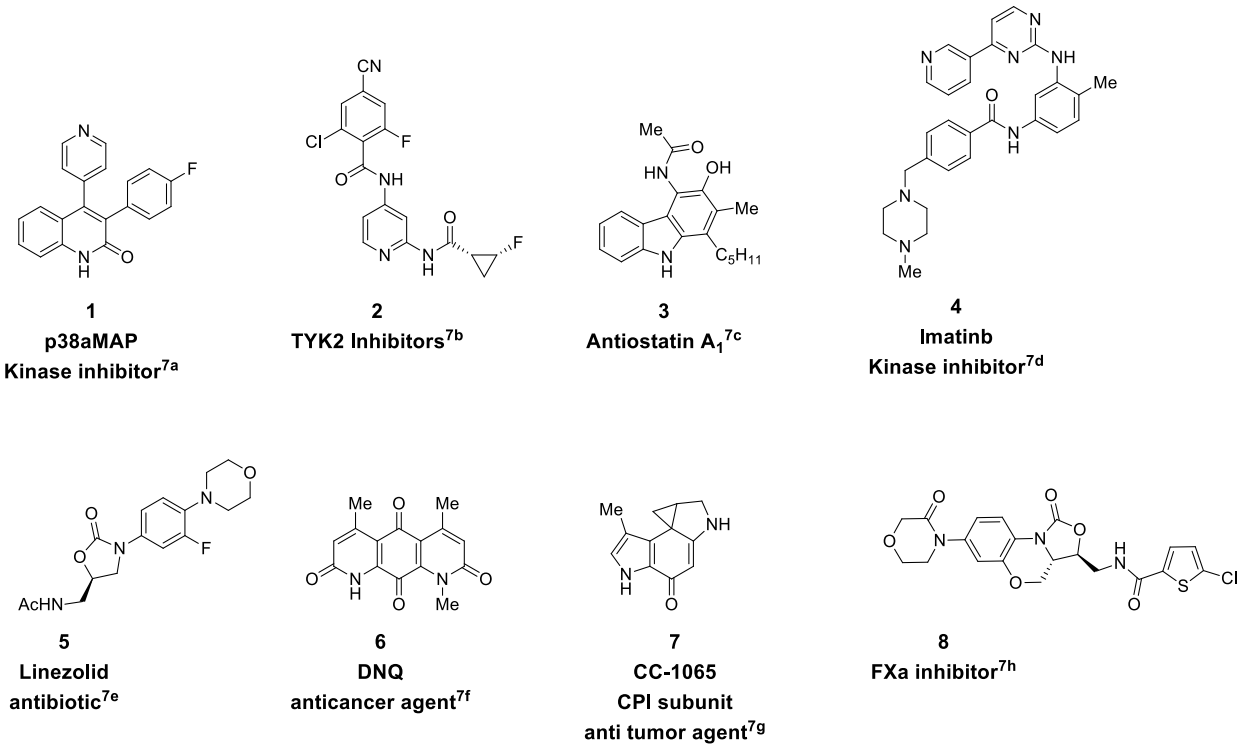


Figure 1. Representative examples of biologically active secondary and tertiary amides.

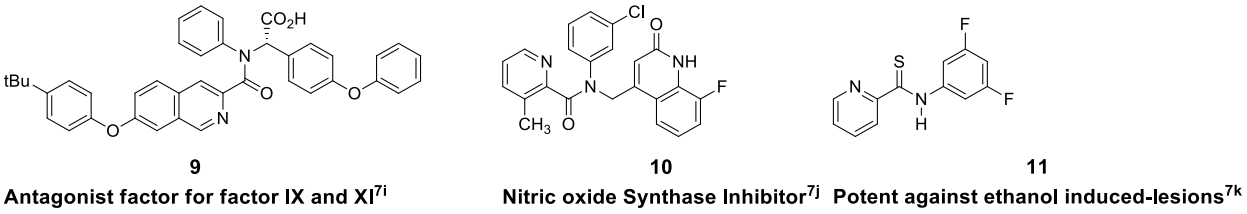
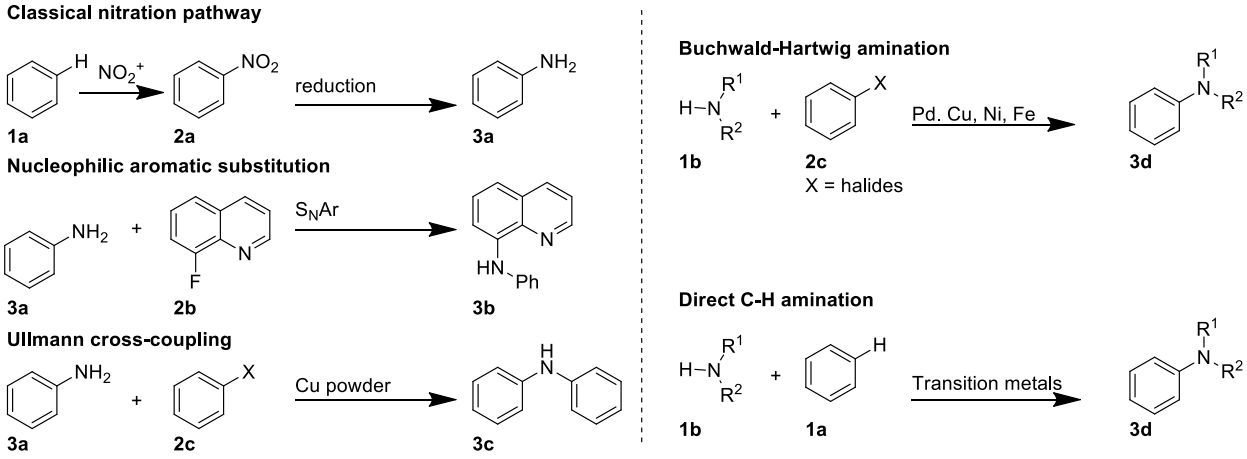
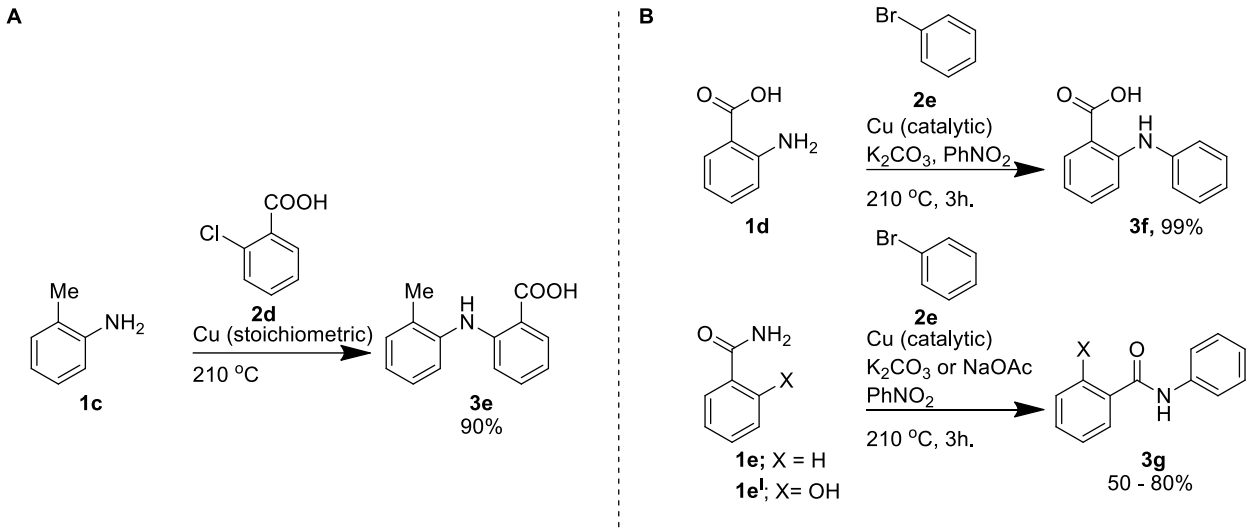


Figure 2. Representative examples of biologically active picolinamides.

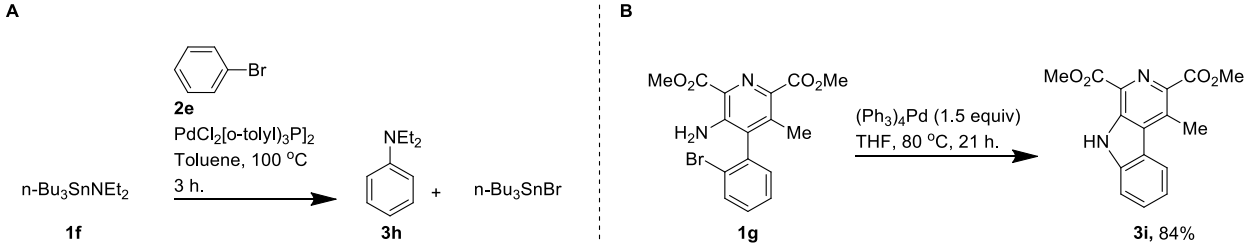


Scheme 1. General amination methods.

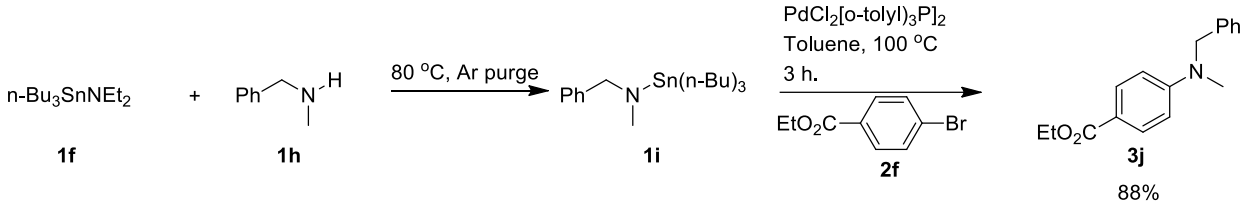


Scheme 2. Fritz Ullmann and Irma Goldberg *N*-arylation reactions.

This work was further developed by Irma Goldberg in 1906 (Scheme 2B).[9b] Initial work reveals the necessity of stoichiometric amount of copper but further studies by Irma Goldberg utilized catalytic amounts of copper. In 1983, Migita and Kosugi reported the palladium catalyzed *N*-arylation using aryl bromides and tributyl (*N*, *N*-diethylamino) tin (**1f**) (Scheme 3A).[10a] This discovery was innovative and useful but it has limitations such as preparation of amine stannane reagents and the formation tributyltin derivative as a side product.



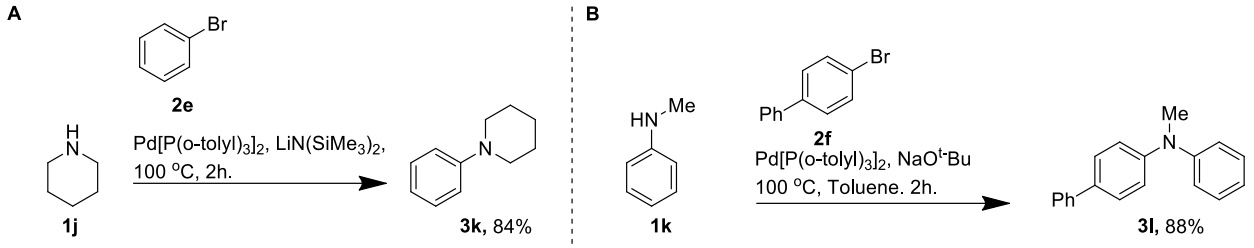
Scheme 3. Palladium-catalyzed *N*-arylation reactions.



Scheme 4. Buchwald work on *N*-arylation of **1h**.

In 1985, Boger and co-workers reported intramolecular *N*-arylation (Scheme 3B).[10b] In 1994 Hartwig and coworkers reported mechanistic studies for the C-N bond formation that helped to

identify the reaction intermediates and to design the catalyst.[10c] Migita's work was further developed by Buchwald and coworkers in 1994 (Scheme 4).[10d]



Scheme 5. Stannane free palladium-catalyzed reactions.

Due to the toxic nature and unstable stannane amine the previous discoveries were not attractive, the further studies on palladium-catalyzed *N*-arylation reaction have led to stannane free amination, was independently developed by Hartwig[10e] and Buchwald[10f] (Scheme 5A and 5B).

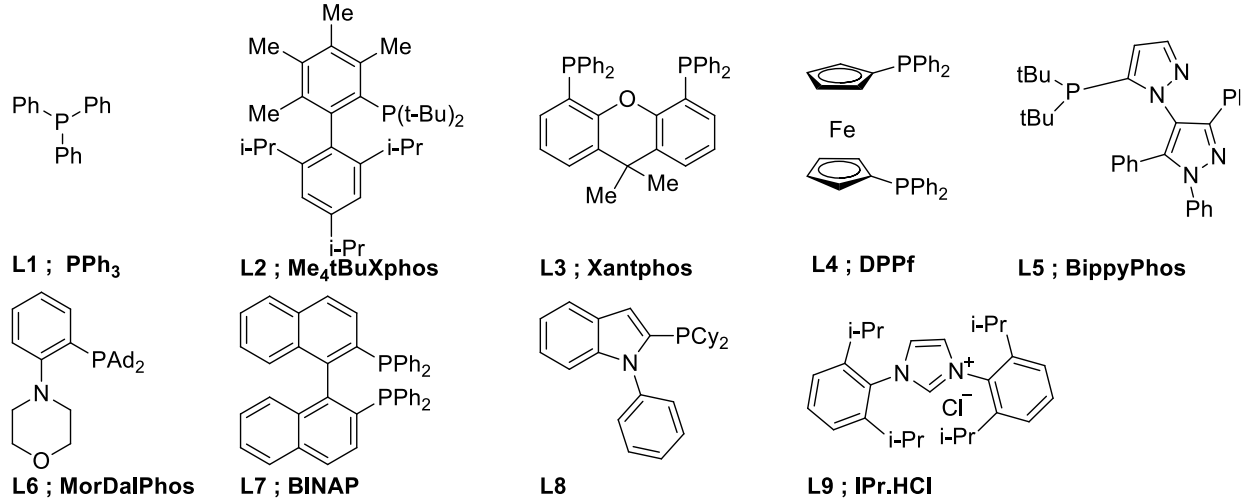
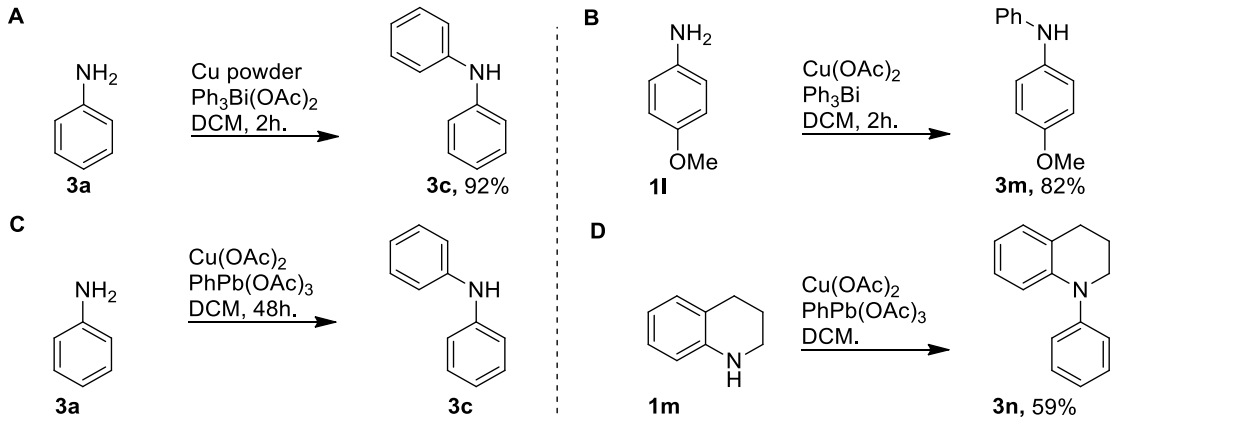
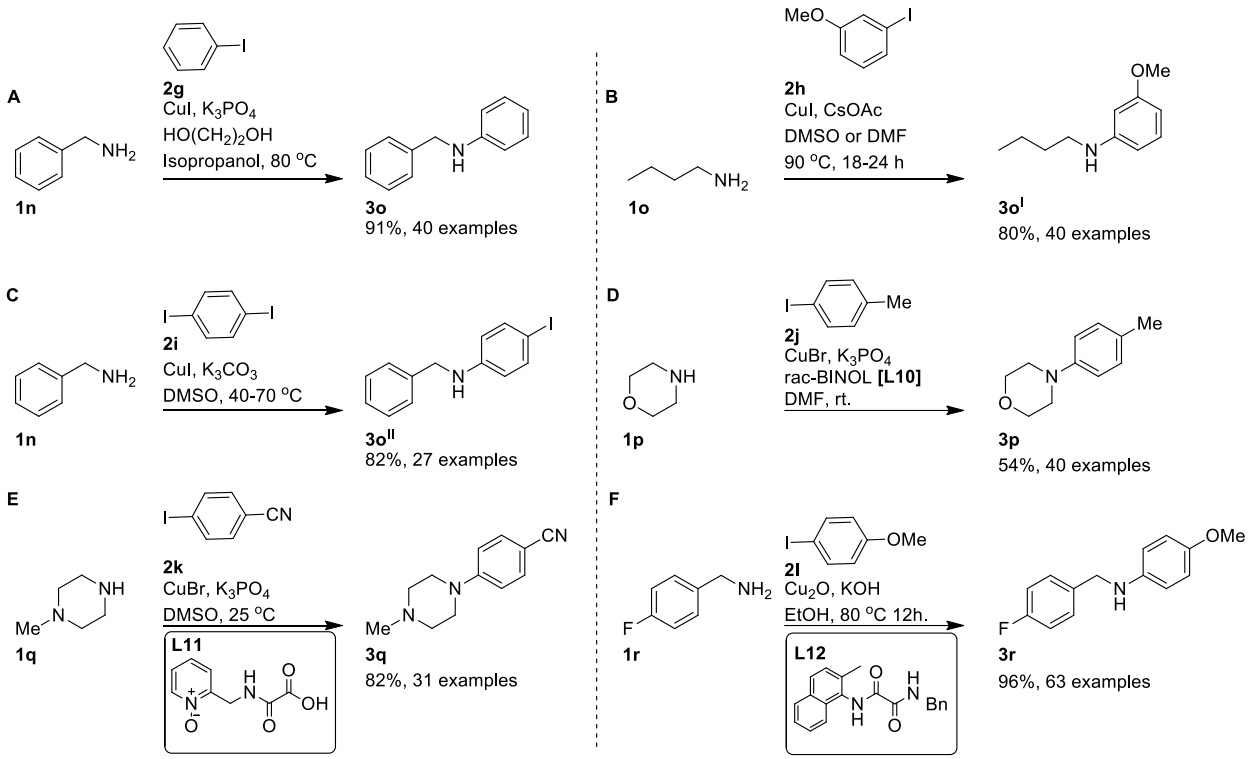


Figure 3. Ligands used in the transition metal catalyzed *N*-arylation of primary/secondary amines and amides.

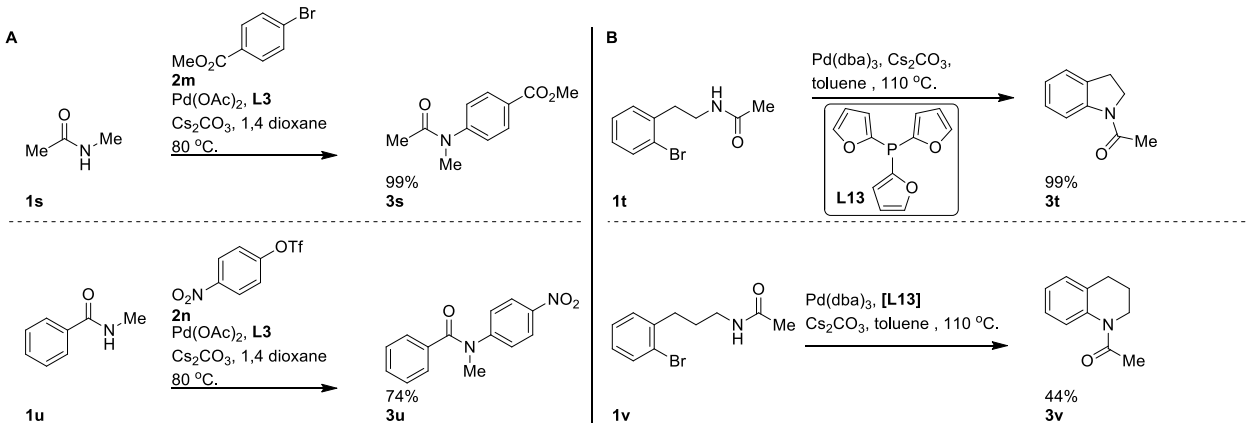


Scheme 6. Barton's work on copper-catalyzed *N*-arylation reactions.

Subsequently, Buchwald and Hartwig and other groups had discovered many synthetic routes to access *N*-aryl molecules by introducing various ligands (Figure 3) with transition metals.[10,11] After Ullmann and Goldberg, further studies on copper-catalyzed *N*-arylation reactions led to various fruitful processes affording amine derivatives shown in Schemes 6 and 7.[12, 13]



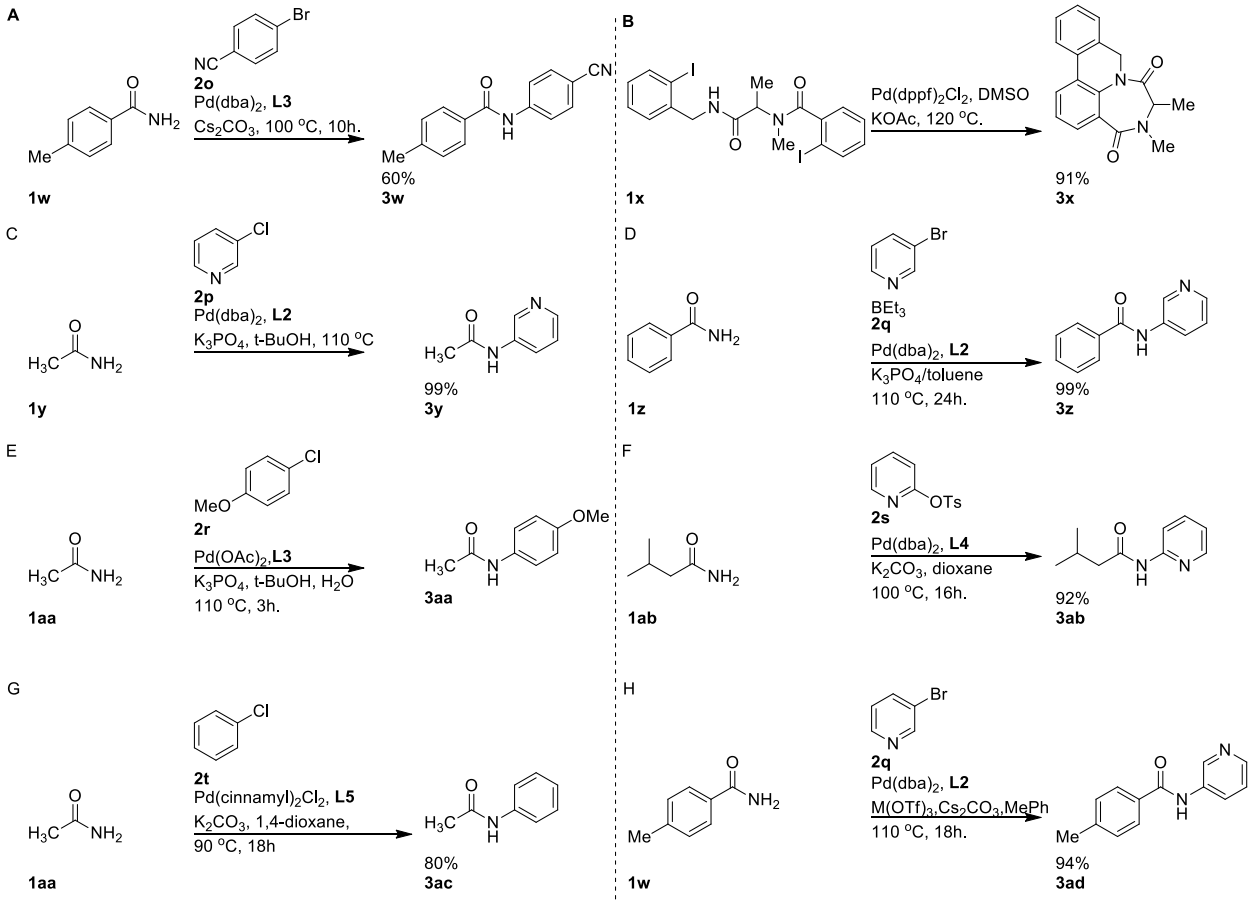
Scheme 7. Copper-catalyzed *N*-arylation reaction conditions.



Scheme 8. Buchwald work on Amide *N*-arylation reactions.

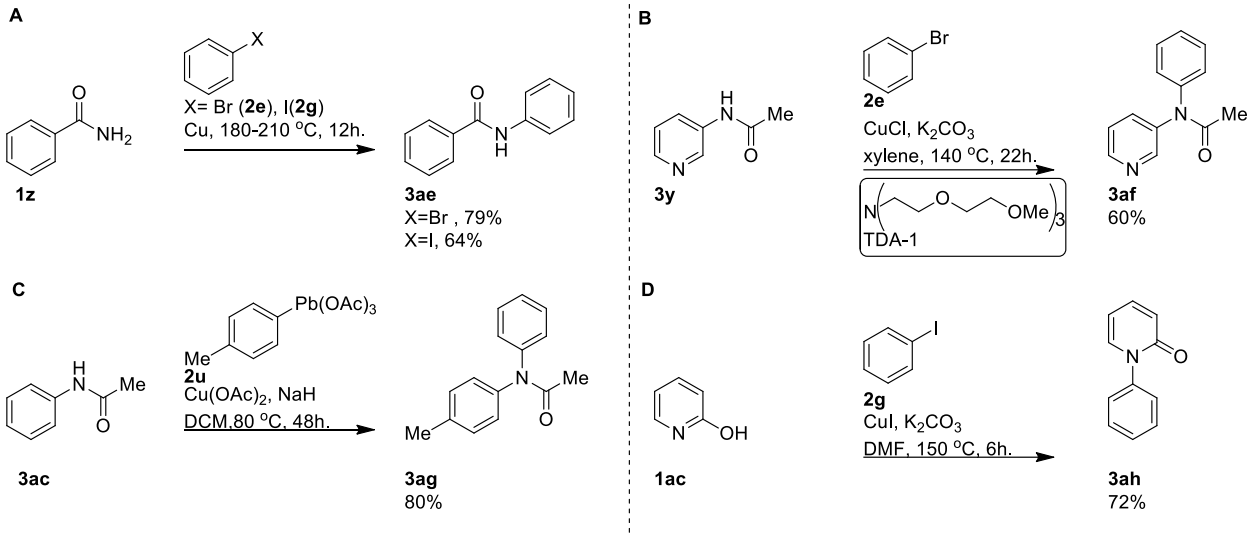
It is to be noted that due to the relatively decreased reactivity of amides, the *N*-arylation of amides are challenging than *N*-arylation primary/secondary amines and anilines. A literature survey revealed that the *N*-arylation and C-N bond formations have been well studied using primary

amides when compared to the *N*-arylation of secondary amides. In 2000, the palladium-catalyzed intermolecular amide *N*-arylation was reported by Buchwald (Scheme 8A)[14a] and previously he described the intramolecular amide *N*-arylation on 1996 (Scheme 8B).[14b] Further, some of the representative palladium-catalyzed *N*-arylation reactions revealing the importance of ligands in the *N*-arylation of amides have been summarized in Scheme 9.[14]

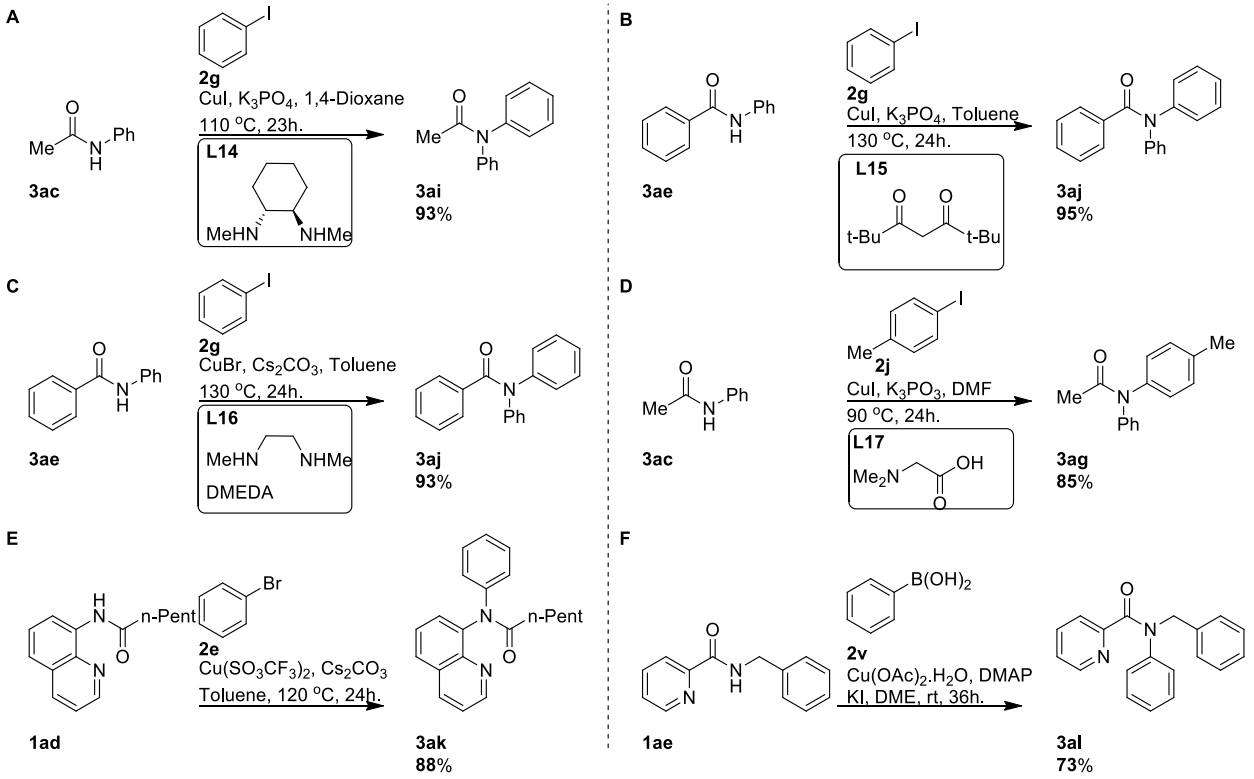


Scheme 9. Palladium-catalyzed *N*-arylation of primary/secondary amides.

In 1982, Yamamoto and Kurata reported copper and copper oxide catalyzed arylation of active hydrogen of functional groups such as imide, amide, aniline, phenol, benzoic acid (Scheme 10A).[15a] Benzamide **1z** was arylated using aryl bromide **2e** and aryl iodide **2g**. In 1989, Greiner reported amidation of *N*-heteroaryl acetamide **3y** with aryl bromide **2e** using copper chloride as catalyst (Scheme 10B).[15b] In 1996, Avendano and co-workers reported the Cu-based *N*-arylation using aryl lead triacetates **2u** with amides (Scheme 10C).[15c] In 1997, Ukita and Co-workers reported the Cu-based arylation of amide heterocycles such as 2-hydroxy pyridine **1ac**, 2-hydroxy quinolone, pyrimidone, pyrrolidone, etc (Scheme 10D).[15d]



Scheme 10. Copper-based *N*-arylation of amides.

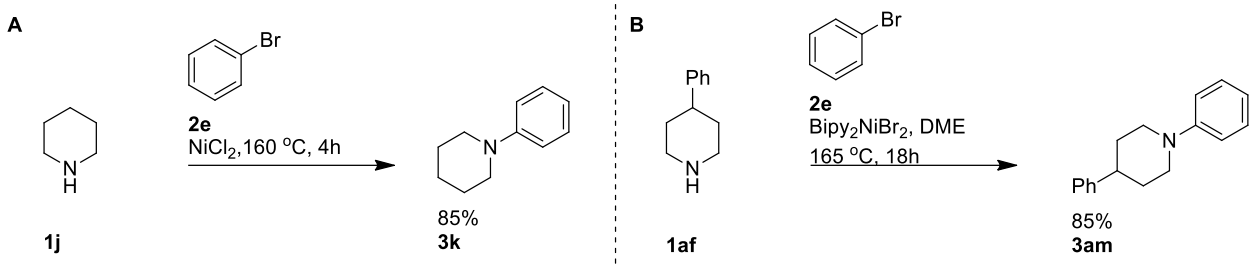


Scheme 11. Copper-based *N*-arylation of secondary amides.

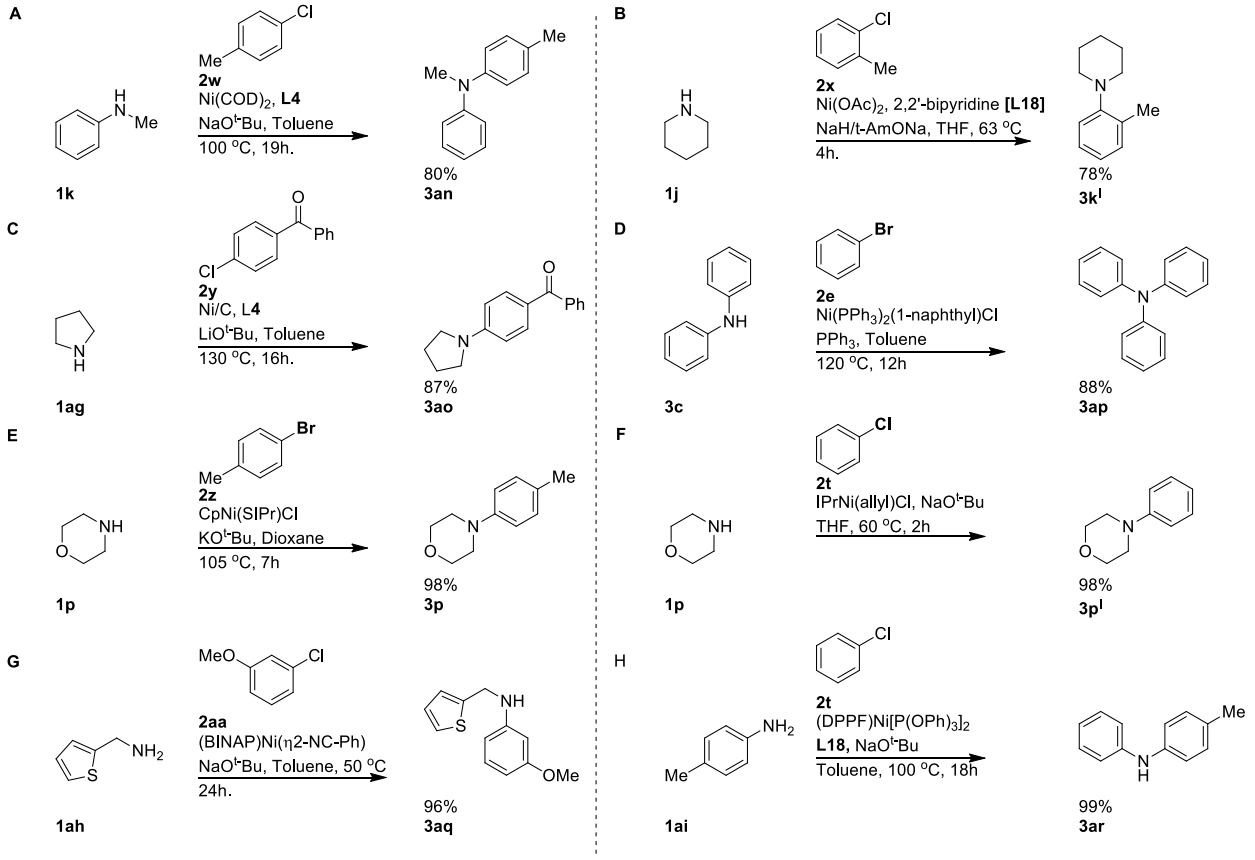
Some of the representative copper-catalyzed *N*-arylation of secondary amides and also revealing the importance of ligands in the *N*-arylation of secondary amides have been summarized in Scheme 11.[16]

The palladium and copper-catalyzed amination and amidation using aryl halides, triflates, metal acetates, mesylates have provided efficient routes for the synthesis of a variety of

primary/secondary/tertiary amines, anilines and amides. The employment of nickel as a catalyst in amination and amidation reaction is also noteworthy choice.[17] The first nickel catalyzed amination reaction was reported by Elersich and Co-workers in 1950.[17b] In 1975, Cramer and Coulson



Scheme 12. Nickel-based *N*-arylation reactions.



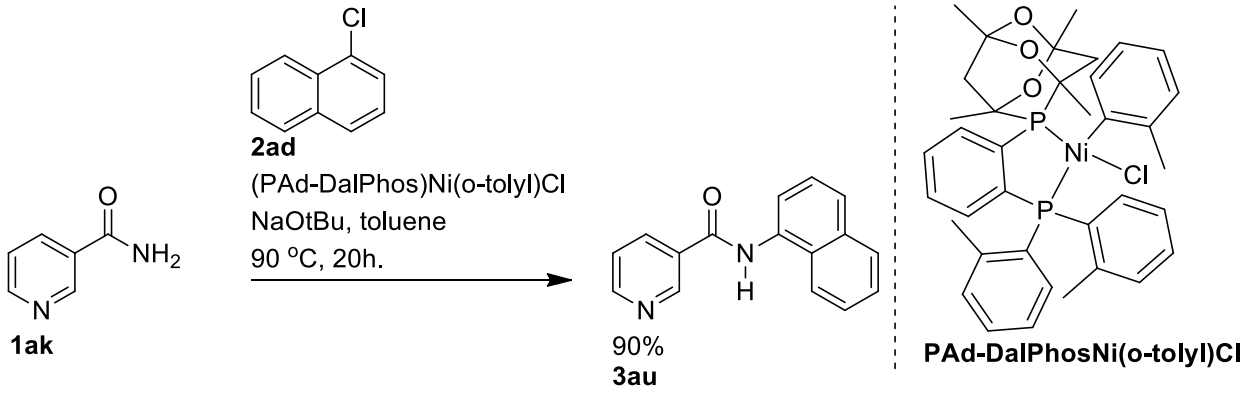
Scheme 13. Nickel-based *N*-arylation reactions.

reported a comprehensive study of the effect of the variation in the reaction conditions and catalyst composition for the nickel-catalyzed amination reaction. The report describes nickel(0) complexes such as [$Ni(CO)_2$ (dppe)] and [$Ni(CO)_2(PPh_3)_2$] showed similar activity to the $NiBr_2$ when used as catalyst for the *N*-arylation of piperidine **1j** with **2e** (Scheme 12A).[17c] Later Cristau and Desmurs reported mechanistic and synthetic studies of palladium, copper, nickel-catalyzed *N*-arylations.

Accordingly, the *N*-arylation of piperidine derivative **1af** with bromobenzene **2e** was described using a nickel catalyst (Scheme 12B).[17d] Some of the further developments and representative nickel-catalyzed *N*-arylation of amines have been summarized in Scheme 13.[17,18]

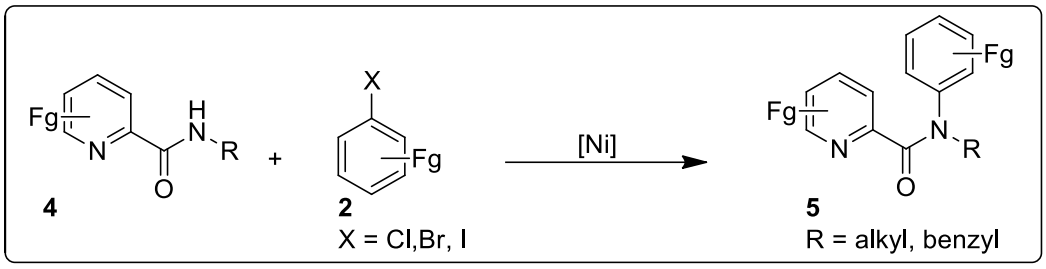
A literature survey revealed that the *N*-arylation and C-N bond formations have been well studied using Cu or Pd catalysts. Notably, the *N*-arylation and C-N bond formations have not been reported using Ni catalysts and especially the usage of nickel catalyst for the synthesis of tertiary amides via *N*-arylation and C-N bond formation has not been explored well. This forms a basis for the present investigation on the usage of nickel catalyst for the synthesis of tertiary amides via *N*-arylation.

During the course of the investigation by our lab on nickel-catalyzed *N*-arylation of secondary amides, recently, Stradiotto and Co-workers reported[18j] the *N*-arylation of primary amide **1ak** and the synthesis of secondary amide **3au** (Scheme 14). However, this report does not deal with the *N*-arylation of secondary amides.



Scheme 14. Nickel-catalyzed *N*-arylation of primary amide.

In recent years, the bidentate directing group (BDG)-assisted C-H functionalization reactions have received a substantial attention.[19] The BDG-assisted C-H functionalization reactions have been explored using Pd, Cu and Ni catalysts.[20,21] In continuation of our lab's interest on the BDG-assisted C-H functionalization reactions,[22] we envisaged to perform the Ni-catalyzed *N*-arylation of 2-picolinamides (acyclic secondary amides, which were derived from 2-picolinic acid and amines) with aryl halides. It was envisaged that in this process, the picolinamide unit will serve as an internal ligand similar to the Cu-catalyzed, *N*-arylation of amides, which were derived from the 8-aminoquinoline BDG and carboxylic acids [23] (Scheme 11F). Accordingly, Chapter 1 reports the nickel-catalyzed tertiary amide synthesis through coupling of secondary amide (2-piconilinamide) with aryl halides (Scheme 15).

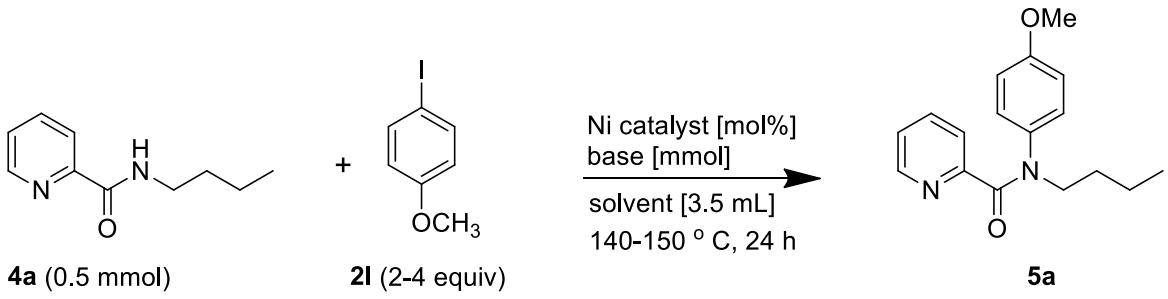


Scheme 15. This work. Nickel-catalyzed *N*-arylation of secondary amides (2-piconilinamides) with aryl halides and synthesis of tertiary amides.

Results and Discussion

To explore the *N*-arylation and the C-N cross-coupling reaction of secondary acyclic amide with aryl halide using a nickel catalyst, we initially performed the optimization reactions using the 2-picolinamide **4a** (prepared from 2-picolinic acid and *n*-butyl amine). Table 1 shows the results of the C-N cross-coupling reaction of **4a** with **2l** in the presence of various Ni catalysts, additives/bases and solvents. Heating the mixture of **4a**, **2l** and Na_2CO_3 without any catalyst in DMF at 140-150 ^oC did not give any product (entry 1, Table 1). Next, heating the mixture of **4a**, **2l** and $NiCl_2$ (10 mol%) without any base in DMF did not give any product (entry 2, Table 1). Then, heating the mixture of **4a**, **2l**, Na_2CO_3 and $NiCl_2$ (10 mol%) in DMF afforded the tertiary amide **5a** in 30% yield (entry 3, Table 1).

Table 1. Optimization Reactions. Ni-Catalyzed *N*-Arylation of **4a** with **2l**.



4a (0.5 mmol) **2l** (2-4 equiv) **5a**

entry	Ni catalyst [10 mol%]	base [mmol]	additive / ligand [mol%]	solvent	**5a**; yield [%]
1	-	Na_2CO_3 [1]	-	DMF	0
2	$NiCl_2$	-	-	DMF	0
3	$NiCl_2$	Na_2CO_3 [1]	-	DMF	30
4	$NiCl_2$	Na_2CO_3 [1]	MesCOOH [20]	DMF	30
5[a]	$NiCl_2$	Na_2CO_3 [1]	-	$MeNO_2$	0

6[a]	$NiCl_2$	Na_2CO_3 [1]	-	DMSO	0
7[a]	$NiCl_2$	Na_2CO_3 [1]	-	MeCN	0
8	$NiCl_2$	K_2CO_3 [1]	-	DMF	14
9	$NiCl_2$	Cs_2CO_3 [1]	-	DMF	0
10	$NiCl_2$	*t*BuONa [1]	-	DMF	21
11	$NiCl_2$	*t*BuOK [1]	-	DMF	40
12	$NiCl_2$	*t*BuOK [1]	$P[Ph]_3$ [10]	DMF	31
13	$NiCl_2$	*t*BuOK [1]	BINAP [10]	DMF	40
14	-	NaH [1.5]	-	DMF	0
15	$NiCl_2$	NaH [0.5]	-	DMF	49
16	$NiCl_2$	NaH [1]	-	DMF	71
17	$NiCl_2$	NaH [1.5]	-	DMF	80
18[b]	$NiCl_2$	NaH [1.5]	-	DMF	<5
19	$NiCl_2 \cdot 6H_2O$	NaH [1.5]	-	DMF	80
20[c]	$NiCl_2 \cdot 6H_2O$	NaH [1.5]	-	DMF	34
21[d]	$NiCl_2 \cdot 6H_2O$	NaH [1.5]	-	DMF	62
22	$Ni[C_5HF_6O_2]_2\, xH_2O$	NaH [1.5]	-	DMF	0
23	$Ni[acac]_2$	NaH [1.5]	-	DMF	0
24[e]	$NiCl_2$	*t*BuONa [1]	TMEDA [10-30]	DMF	<15
25[e]	$NiCl_2$	*t*BuONa [1]	DMEDA [10]	DMF	0
26[e]	$NiCl_2$	NaH [1.5]	TMEDA [10]	DMF	0
27[e]	$NiCl_2$	Na_2CO_3 [1]	TMEDA [10]	DMF	0

[a] Reaction was performed at the boiling point of solvent used. [b] Reaction was performed at 100 ^oC. [c] **2l** = 0.5 mmol (1 equiv). [d] **2l** = 1 mmol (2 equiv). [e] Reactions were performed using the substrate **4b** instead of **4a**.

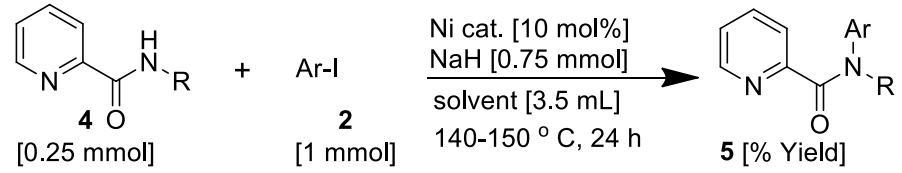
Encouraged by this result, we performed the reaction of **4a** and **2l** in the presence of Na_2CO_3 and MesCOOH as an additive, which afforded **5a** in 30% yield (entry 4, Table 1). We then performed the reaction of **4a** and **2l** in other solvents (e.g., $MeNO_2$, DMSO and MeCN) and other bases (e.g., K_2CO_3 and Cs_2CO_3) and these reactions were not fruitful (entries 5-9, Table 1). The Ni-catalyzed reaction of **4a** and **2l** in the presence of *t*-BuONa or *t*-BuOK afforded **5a** in 21-40% yields (entries 10 and 11, Table 1). The Ni-catalyzed reaction of **4a** and **2l** in the presence of *t*-BuONa and

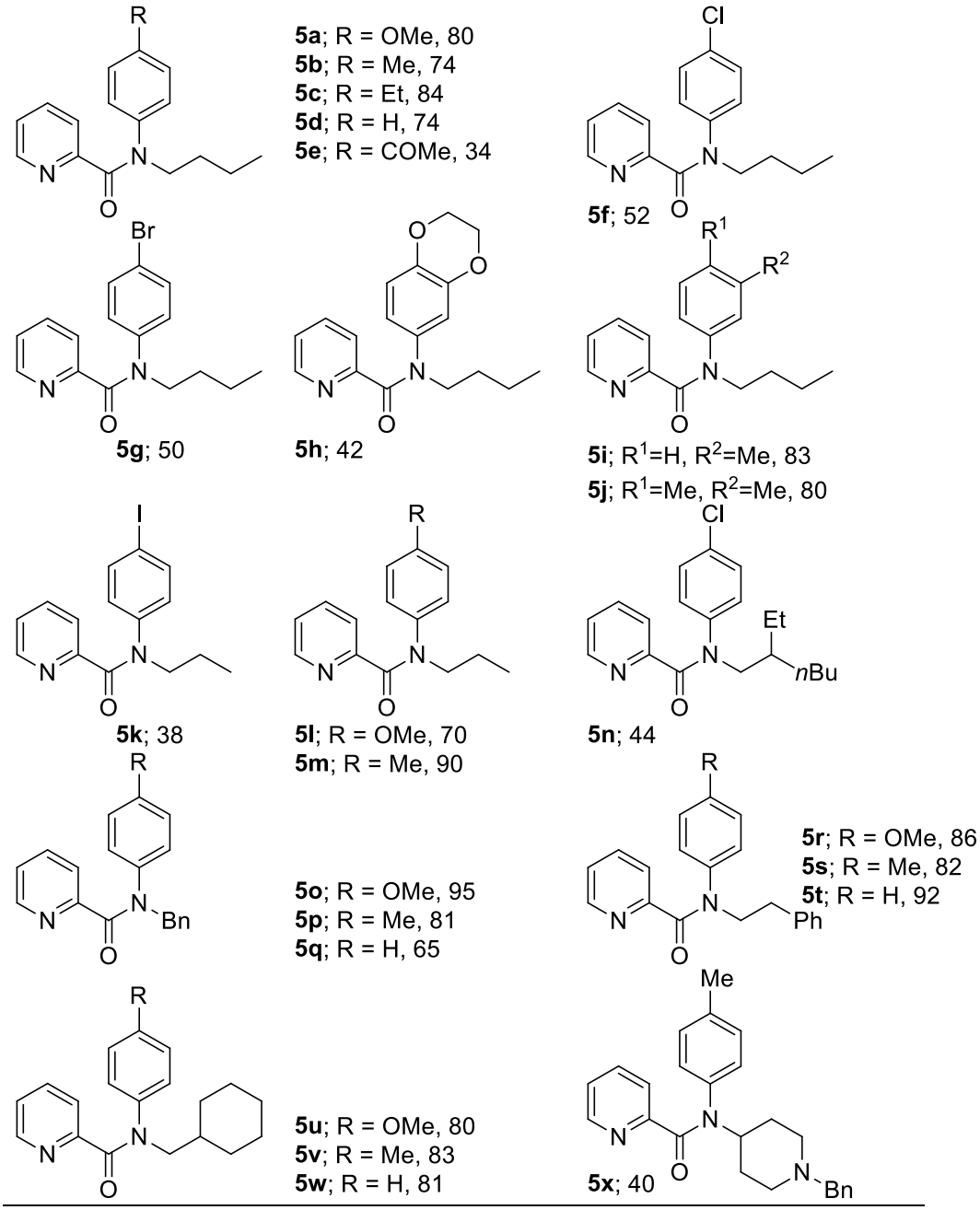
phosphine ligands P[Ph]$_3$ or BINAP afforded **5a** in 31-40% yields (entries 12 and 13, Table 1). Next, to improve the yield of **5a**, we wished to use NaH as the base to perform the *N*-arylation of **4a**. In this regard, initially we performed the reaction of **4a** and **2l** in the presence of NaH without any Ni catalyst and this reaction did not give the product **5a** (entry 14, Table 1). Next, heating the mixture of **4a** (1 equiv), **2l** (4 equiv), NaH (1-3 equiv) and $NiCl_2$ (10 mol%) in DMF at 140-150 ^oC for 24 h afforded **5a** in 49-80% yields (entries 15-17, Table 1). Heating the mixture of **4a**, **2l**, NaH and $NiCl_2$ (10 mol%) in DMF at 100 ^oC afforded **5a** in only <5% yield (entry 18, Table 1). Next, we performed the *N*-arylation of **4a** (1 equiv) with **2l** (4 equiv) using NaH (3 equiv) and $NiCl_2{\cdot}6H_2O$ (10 mol%) as the catalyst instead of $NiCl_2$ catalyst. This reaction afforded **5a** in 80% yield (entry 19, Table 1). The Ni-catalyzed *N*-arylation of **4a** (1 equiv) using 1-2 equivalents of **4a** afforded **5a** in 34-62% yields (entries 20 and 21, Table 1). The reaction of **4a** and **2l** in the presence of other Ni catalysts, such as $Ni[C_5HF_6O_2]_2 \cdot xH_2O$ and Ni[acac]$_2$ and usage of chelating ligands e.g., DMEDA or TMEDA were also not fruitful (entries 22-27, Table 1).

Next, we wished to test the generality of this Ni-catalyzed *N*-arylation method using various secondary acyl amides and different aryl iodides. Accordingly, various picolinamides were treated with different aryl iodides in the presence of $NiCl_2$ or $NiCl_2{\cdot}6H_2O$ catalyst under the optimized reaction conditions (entries 17 and 19, Table 1). At first, we performed the Ni-catalyzed *N*-arylation of **4a** with PhI and different aryl iodides containing electron donating and withdrawing substituents (e.g., OMe, Me, Et and COMe) at the *para* position in the aryl ring, which afforded the corresponding tertiary amides **5a-e** in 34-84% yields (Table 2). We then performed the Ni-catalyzed *N*-arylation of **4a** with aryl iodides containing Cl and Br substituents at the *para* position in the aryl ring. These reactions afforded the corresponding tertiary amides **5f** (52%) and **5g** (50%) in which Cl and Br substituents were found to be intact. Next, we performed the Ni-catalyzed *N*-arylation of **4a** with different di-substituted aryl iodides, which afforded the corresponding tertiary amides **5h-j** in 42-83% yields (Table 2).

Subsequently, we prepared various picolinamides **4b-g** and subjected them to the Ni-catalyzed C-N coupling reaction conditions. Accordingly, the Ni-catalyzed *N*-arylation of **4b-g** with different aryl iodides afforded the corresponding tertiary amides **5k-x** in 38-95% yields (Table 2).

Table 2. Ni-Catalyzed *N*-Arylation of Secondary Amides with ArI.[a-c]





[a] $NiCl_2$ was used to obtain **5a-m**. [b] $NiCl_2 \cdot 6H_2O$ was used to obtain **5n-x**. [c] **5a-j**, **5k-m** and **5n** were obtained from **4a**, **4b** and **4c**, respectively. **5o-q**, **5r-t**, **5u-w** and **5x** were obtained from **4d**, **4e**, **4f** and **4g**, respectively.

The substituents e.g., I and Cl were intact in **5k** and **5n** and the products **5k**, **5n** and **5x** were obtained in low yields and this might be due to some specific reasons, which are not clear at this stage. Since the corresponding *N*-arylation reactions were performed using aryl iodides containing I and Cl substituents, there might be some side reactions. However, apart from the products **5k** and **5n**, we did not get any other side products in characterizable amounts.

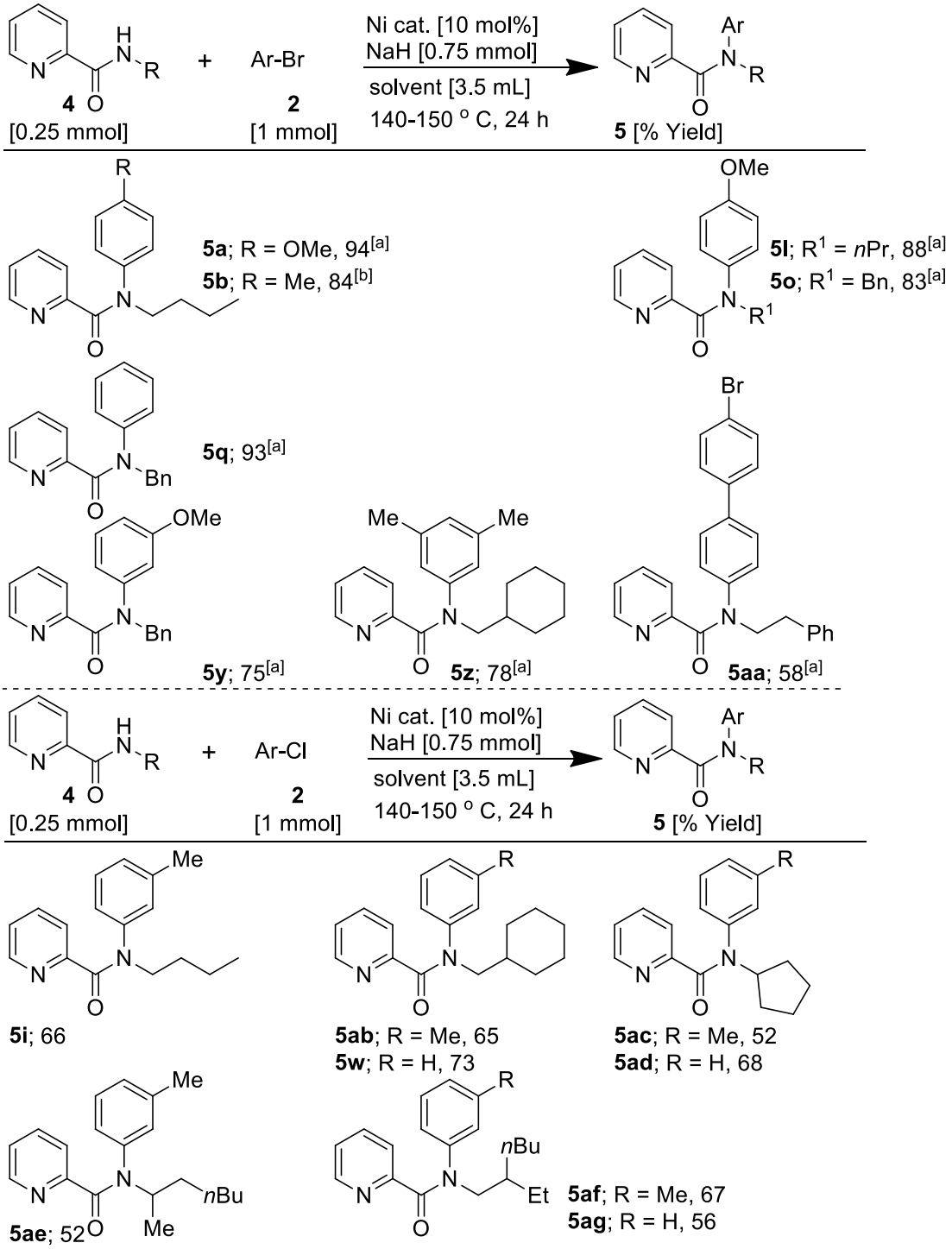
Having done the Ni-catalyzed *N*-arylation of various picolinamides using different aryl iodides, next we wished to extend the value of this Ni-catalyzed *N*-arylation and C-N cross-coupling reaction of secondary amides using aryl bromides and chlorides as the coupling partners. Table 3 shows the results of the Ni-catalyzed *N*-arylation of picolinamides with different aryl bromides and chlorides. Accordingly, the tertiary amides **5a**/**5b**, and **5l** were obtained in 84-94% yields from the corresponding Ni-catalyzed *N*-arylation of picolinamides with aryl bromides (Table 3). The tertiary amides **5o**, **5y** and **5q** were obtained in 75-93% yields from the corresponding Ni-catalyzed *N*-arylation of picolinamide **4d** and aryl bromides (Table 3). Similarly, the tertiary amides **5z** and **5aa** were obtained in 58-78% from the corresponding Ni-catalyzed *N*-arylation of picolinamides **4f** and **4e** with aryl bromides (Table 3).

Next, the tertiary amides **5i**, **5ab** and **5w** were also obtained in 65-73% yields from the corresponding Ni-catalyzed *N*-arylation of the picolinamides **4a** and **4f** with aryl chlorides (Table 3). Finally, the tertiary amides **5ac**, **5ad**, **5ae**, **5af** and **5ag** were obtained in 52-68% yields from the corresponding Ni-catalyzed *N*-arylation of the picolinamides **4h, 4i** and **4c** with aryl chlorides (Table 3). The Ni-catalyzed *N*-arylation of 3-methyl-2-picolinamide **4j** with **2l** also afforded the product **5ah** in 41% yield (Scheme 16).

Except for some specific cases, the yields obtained in the Ni-catalyzed *N*-arylation of picolinamides using aryl iodides and aryl bromides were comparable and the corresponding tertiary amides were obtained in good to excellent yields. On the other hand, while the Ni-catalyzed *N*-arylations of picolinamides with aryl chlorides were successful, satisfactory yields were obtained in the Ni-catalyzed *N*-arylation of picolinamides using aryl chlorides. We also attempted the removal of the picolinamide unit using a representative tertiary amide **5l**. Accordingly, the amide hydrolysis reaction of **5l** afforded the secondary amine **6** in 76% yield (Scheme 16). We performed some control experiments to apprehend the role of the 2-picolinamide unit in the Ni-catalyzed *N*-arylations of amides **4a-j** with aryl halides. Accordingly, the Ni-catalyzed *N*-

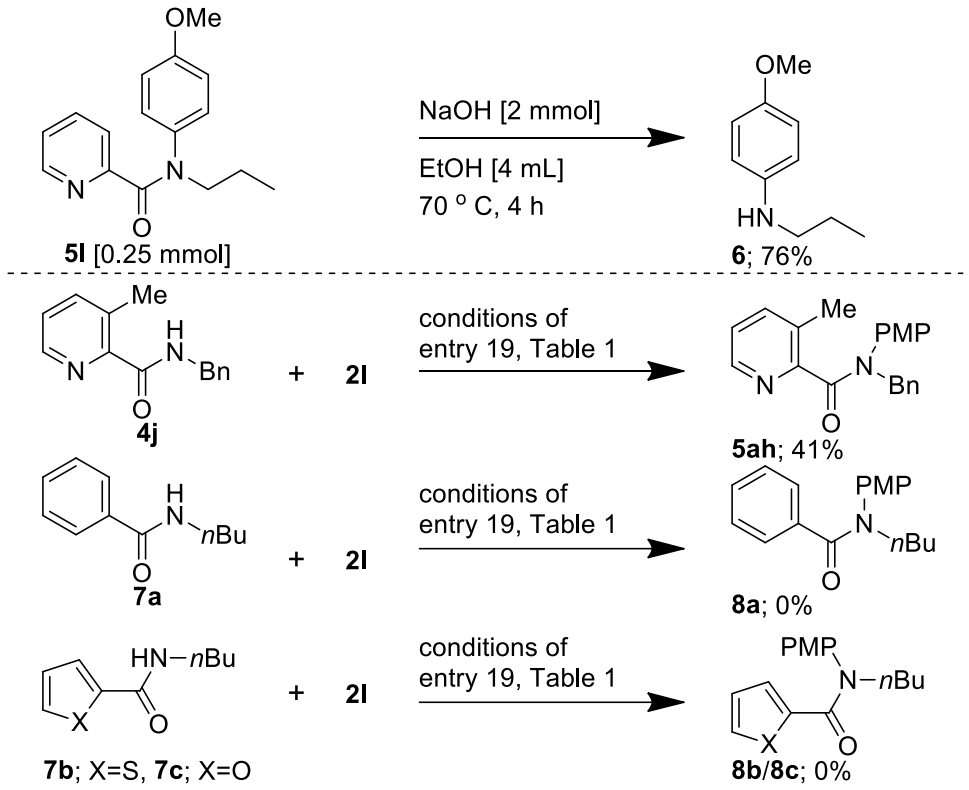
arylations of amides **7a-c** with **2l** did not give the corresponding tertiary amides in characterizable amounts (Scheme 16).

Table 3. Ni-Catalyzed *N*-Arylation of Secondary Amides with ArBr/ArCl.[a-c]

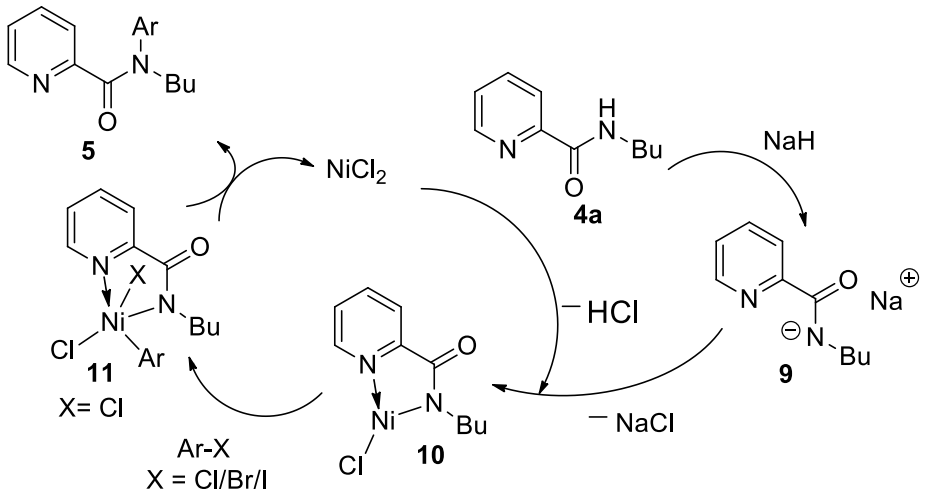


[a] $NiCl_2 \cdot 6H_2O$ was used. [b] $NiCl_2$ was used. [c] **5a**/**5b** and **5l** were obtained from **4a** and **4b**, respectively. **5o**/**5y**/**5q** were obtained from **4d**. **5z**, and **5aa** were obtained from **4f** and **4e**, respectively. **5i** and **5ab**/**3w**

were obtained from **4a** and **4f**, respectively. **5ac**/**5ad**, **5ae** and **5af**/**5ag** were obtained from **4h**, **4i** and **4c**, respectively.



Scheme 16. *N*-Arylation of **4j**, **7a-c** and Hydrolysis of picolinamide **5l**.



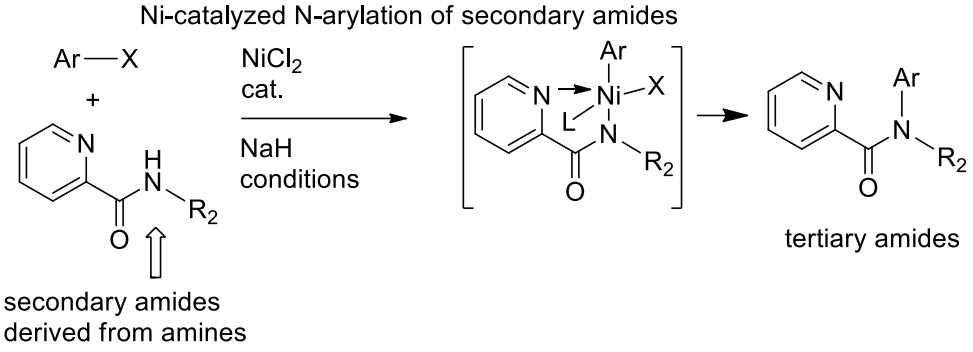
Scheme 17. A Plausible Mechanism for the Ni-Catalyzed *N*-Arylation of **1a**.

It is well known that the bidentate directing group served as a chelating ligand in the Ni-catalyzed C-H functionalization reactions. In concurrence with the Cu-catalyzed *N*-arylation of amides, in which the 8-aminoquinoline BDG unit served as an internal ligand and based on the control

experiments, a plausible mechanism is proposed for the Ni-catalyzed *N*-arylation of picolinamides with aryl halides (Scheme 17).

Summary

In summary, the work shown in this chapter 1 disclosed the nickel-catalyzed tertiary amide synthesis via the *N*-arylations of various picolinamides. This protocol employs least expensive and air-stable $NiCl_2$ or $NiCl_2 \cdot 6H_2O$ catalysts. The metal catalyst does not utilize any external ligand for C-N coupling process since the bidentate directing group picolinamide unit served as an internal chelating ligand in the Ni-catalyzed *N*-arylations.



General methods.

IR spectra of all compounds were recorded as thin films or KBr pellets. ^1H and ^{13}C NMR spectra of all compounds were recorded (using TMS as an internal standard) in 400 MHz and 100 MHz spectrometers, respectively. The HRMS measurements were obtained from QTOF mass analyzer using electrospray ionization (ESI) method. Column chromatography was carried out on silica gel (100-200 mesh, eluent; EtOAc: hexane). Reactions were performed in an anhydrous solvent under a nitrogen atmosphere wherever necessary. Solutions were dried using anhydrous Na_2SO_4. Thin layer chromatography analysis was performed on silica gel/alumina plates and components were visualized by observation under iodine. Isolated yields of all the compounds were reported and yields were not optimized. The ^1H NMR signals for some of the amides were obtained as broad signals.

General Procedure for preparation of picolinamides 4:

To an oven dried double neck RB flask (50 mL capacity), picolinic acid (1.85 g, 15 mmol, 1 equiv), DCM (30 mL) DMF (3 drops), was added under a nitrogen atmosphere. Next, to the reaction mixture, oxalyl chloride (2.25g, 1.2 equiv) was added drop wise at 0 ^oC. Then, the reaction mixture was stirred at room temperature for 5 h. After this period the solvent was removed under reduced

pressure vacuum and the resulting acid chloride was used in the next step without further purification. To another oven dried double neck RB flask (100 mL capacity), *n*-butyl amine (1.43g, 1.3 equiv), triethylamine (3.04 g, 2 equiv) and DCM (30 mL) were added. Then, to this reaction mixture was added the acid chloride dissolved in DCM (5-8 mL) at 0 ^{o}C. Then, the mixture was stirred at rt for 12 h. After this period, the reaction mixture was quenched with saturated aqueous $NaHCO_3$ (30 mL) and the organic layer was separated, further the aqueous solution was extracted with DCM (2×20 mL). The combined organic layers were washed with brine (30 mL) and dried over anhydrous Na_2SO_4 and concentrated in vacuum to afford a crude reaction mixture. Then, the crude reaction mixture was purified by silica gel column (100-200 mesh, eluent; EtOAc: hexane) to afford the corresponding picolinamides **4, 7**.

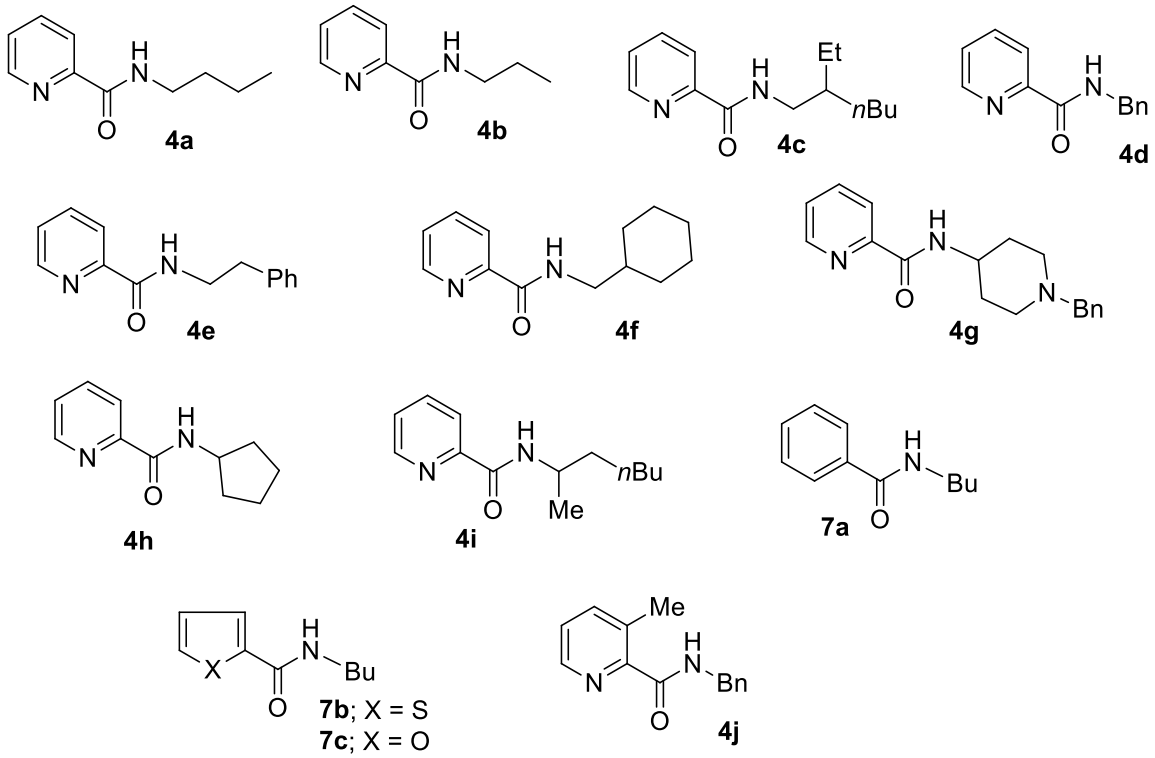
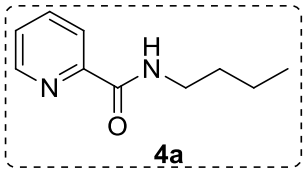


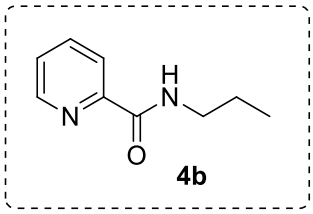
Figure 4. Secondary amide starting materials used for the synthesis of corresponding tertiary amide via the Ni-catalyzed *N*-arylation of picolinamides.

***N*-Butylpicolinamide (4a**): Following the general procedure, **4a** was obtained after purification by column chromatography on silica gel (EtOAc:hexane = 1:4) as a brown oil; R_f = 0.6 (EtOAc:hexane = 1:4); yield: 94% (2.51 g); IR (KBr): 3377, 2959, 1669, 1529 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.55–8.54 (m, 1H), 8.22–8.20 (m, 1H), 8.07 (br s, 1H), 7.86 (td, 1H, J_1

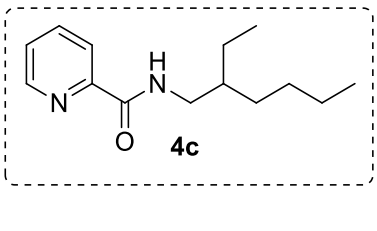


= 7.7 Hz, J_2 = 1.2 Hz), 7.45–7.41 (m, 1H), 3.50 (q, 2H, J = 7.1 Hz), 1.67–1.60 (m, 2H), 1.49–1.39 (m, 2H), 0.97 (t, 3H, J = 7.3 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 164.2, 150.0, 148.0, 137.3, 126.0, 122.1, 39.1, 31.7, 20.1, 13.8; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{10}H_{15}N_2O$: 179.1184; found 179.1186.

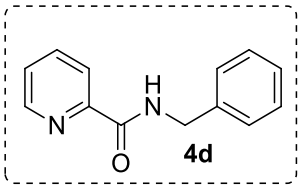
***N*-Propylpicolinamide (4b)**: Following the general procedure, **4b** was obtained after purification by column chromatography on silica gel (EtOAc:hexane = 1:4) as a brown oil; R_f = 0.6 (EtOAc:hexane = 1:4); yield: 98% (2.41 g); IR (KBr): 3387, 2967, 1668, 1590 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.52 (dd, 1H, J_1 = 4.8 Hz, J_2 = 0.8 Hz), 8.19 (d, 1H, J = 7.8 Hz), 8.10 (br s, 1H), 7.84–7.80 (m, 1H), 7.42–7.40 (m, 1H), 3.42 (q, J = 6.9 Hz), 1.67-1.62 (m, 2H), 0.98 (t, 3H, J = 7.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 164.3, 150.0, 148.0, 137.4, 126.1, 122.2, 41.1, 22.9, 11.5; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_9H_{13}N_2O$: 165.1028; found 165.1027.



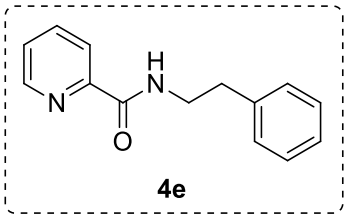
***N*-(2-Ethylhexyl)picolinamide (4c):** Following the general procedure, **4c** was obtained after purification by column chromatography on silica gel (EtOAc:hexane = 1:4) as colorless oil; R_f = 0.7 (EtOAc:hexane = 1:4); yield: 83% (2.91 g); IR (KBr): 3392, 2928, 1677, 1527 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.56–8.54 (m, 1H), 8.21 (d, 1H, J = 7.8 Hz), 8.09 (br s, 1H), 7.85 (td, 1H, J_1 = 7.7 Hz, J_2 = 1.7 Hz), 7.44–7.40 (m, 1H), 3.48–3.37 (m, 2H), 1.62–1.56 (m, 1H), 1.44–1.29 (m, 8H), 0.94 (t, 3H, J = 7.4 Hz), 0.90 (t, 3H, J = 6.9 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 164.3, 150.1, 148.0, 137.3, 126.0, 122.2, 42.2, 39.6, 31.1, 28.9, 24.3, 23.0, 14.1, 10.9; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{14}H_{23}N_2O$: 235.1810; found 235.1815.



***N*-Benzylpicolinamide (4d)**: Following the general procedure, **4d** was obtained after purification by column chromatography on silica gel (EtOAc:hexane = 1:4) as a colorless solid; R_f = 0.4 (EtOAc:hexane = 1:4); yield: 86% (2.73 g); IR (KBr): 3372, 2964, 1668, 1530 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.53 (d, 1H, J = 4.2 Hz), 8.43 (br s, 1H), 8.26 (d, 1H, , J = 7.8 Hz), 7.86 (td, 1H, J_1 = 7.7 Hz, J_2 = 1.6 Hz), 7.44–7.30 (m, 6H), 4.69 (d, 2H, J = 6.1 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 164.3, 149.8, 148.1, 138.2, 137.4, 128.7, 127.9, 127.5, 126.3, 122.4, 43.5; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{13}H_{13}N_2O$: 213.1028; found 213.1031.

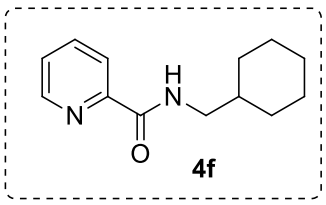


***N*-Phenethylpicolinamide (4e)**: Following the general procedure, **4e** was obtained after purification by column chromatography on silica gel (EtOAc:hexane = 1:4) as a brown oil; R_f = 0.4 (EtOAc:hexane = 1:4); yield: 85% (3.01 g); IR (KBr): 3380, 2931, 1671, 1526 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 8.53 (d, 1H, J = 4.6 Hz), 8.20 (d, 1H, J = 7.8 Hz), 8.18 (br s, 1H), 7.85 (td, 1H, J_1 = 7.7 Hz, J_2 = 1.4 Hz), 7.42 (dd, 1H, J_1 = 7.5 Hz, J_2 = 4.8 Hz), 7.35–7.20 (m, 5H), 3.76 (q, 2H, J = 6.9 Hz), 2.97 (t, 2H, J = 7.3 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 164.3, 149.9, 148.1, 139.0, 137.3, 128.8, 128.6, 126.5, 126.1, 122.2, 40.7, 36.0; HRMS (ESI): *m/z* [M + H]$^+$ calcd for $C_{14}H_{15}N_2O$: 227.1184; found 227.1189.



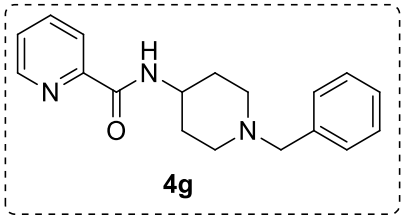
4e

***N*-(Cyclohexylmethyl)picolinamide (4f)**: Following the general procedure, **4f** was obtained after purification by column chromatography on silica gel (EtOAc:hexane = 1:4) as a colorless solid; R_f = 0.6 (EtOAc:hexane = 1:4); yield: 82% (2.68 g); IR (KBr): 3377, 2924, 1670, 1529 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 8.56–8.55 (m, 1H), 8.23–8.20 (m, 1H), 8.14 (br s, 1H), 7.87 (td, 1H, J_1 = 7.7 Hz, J_2 = 1.7 Hz), 7.44–7.41 (m, 1H), 3.33 (t, 2H, J = 6.6 Hz), 1.84–1.57 (m, 6H), 1.31–1.13 (m, 3H), 1.07–0.98 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 164.2, 150.1, 148.0, 137.3, 126.0, 122.0, 45.7, 38.1, 30.9, 26.4, 25.9; HRMS (ESI): *m/z* [M + H]$^+$ calcd for $C_{13}H_{19}N_2O$: 219.1497; found 219.1509.



4f

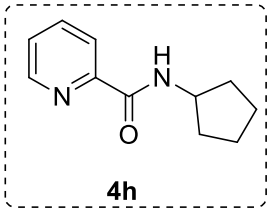
***N*-(1-Benzylpiperidin-4-yl)picolinamide (4g):** Following the general procedure, **4g** was obtained after purification by column chromatography on alumina gel (EtOAc:hexane = 40:60) as a colorless solid; R_f = 0.15 (EtOAc:hexane = 1:4); yield: 87% (3.85 g); IR (KBr): 3379, 2938, 1670, 1521 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 8.55–8.53 (m, 1H), 8.21–8.19 (m, 1H), 8.01 (d, 1H, J = 7.9 Hz), 7.83 (td, 1H, J_1 = 7.7 Hz, J_2 = 1.7 Hz), 7.42–7.38 (m, 1H), 7.35–7.30 (m, 4H), 7.29–7.23 (m, 1H), 4.05–3.98 (m, 1H), 3.52 (s, 2H), 2.87-2.84 (m, 2H), 2.20 (t, 2H, , J = 10.0 Hz), 2.04–1.99 (m, 2H), 1.70–1.60 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 163.5, 150.0, 148.0, 138.5, 137.3, 129.1, 128.2, 127.0, 126.1, 122.2, 63.1, 52.3, 46.5, 32.2; HRMS (ESI): *m/z* [M + H]$^+$ calcd for $C_{18}H_{22}N_3O$: 296.1763; found 296.1784.



4g

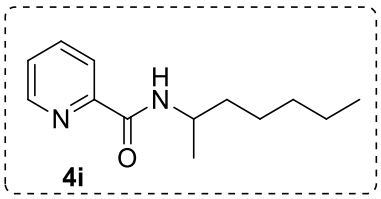
***N*-Cyclopentylpicolinamide (4h):** Following the general procedure, **4h** was obtained after purification by column chromatography on silica gel (EtOAc:hexane = 1:4) as a colorless solid; R_f = 0.6 (EtOAc:hexane = 1:4); yield: 80% (2.28 g); IR (KBr): 3311, 2959, 1654, 1524 cm^{-1}; ^1H NMR

(400 MHz, $CDCl_3$): δ 8.50 (d, 1H, J = 4.6 Hz), 8.16 (d, 1H, J = 7.8 Hz), 7.98 (br s, 1H), 7.83–7.78 (m, 1H), 7.39–7.36 (m,1H), 4.42–4.33 (m,1H), 2.07–2.01 (m, 2H), 1.75- 1.49 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 163.8, 150.1, 147.9, 137.3, 126.0, 122.1, 51.0, 33.1, 23.8; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{11}H_{15}N_2O$: 191.1184; found 191.1189.



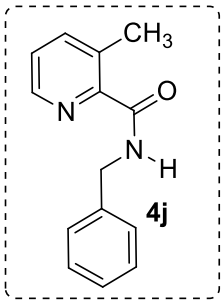
4h

***N*-(Heptan-2-yl)picolinamide (4i):** Following the general procedure, **4i** was obtained after purification by column chromatography on silica gel (EtOAc:hexane = 1:4) as colorless oil; R_f = 0.8 (EtOAc:hexane = 1:4); yield: 89% (2.94 g); IR (KBr): 3380, 2930, 1673, 1521 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.53–8.52 (m,1H), 8.19 (dd, 1H, J_1 = 7.8 Hz, J_2 = 0.9 Hz), 7.87 (d, 1H, J = 7.8 Hz), 7.84–7.80 (m, 1H), 7.41–7.37 (m,1H), 4.21–4.10 (m, 1H), 1.61–1.48 (m, 2H), 1.37–1.23 (m, 9H), 0.85 (t, 3H, J = 5.7 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 163.5, 150.1, 147.9, 137.3, 126.0, 122.2, 45.3, 37.0, 31.7, 25.8, 22.5, 21.0, 14.0; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{13}H_{21}N_2O$: 221.1654; found 221.1660.



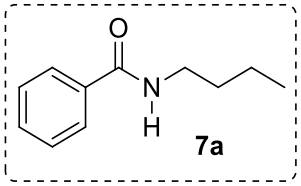
4i

***N*-Benzyl-3-methylpicolinamide (4j):** Following the general procedure, **4j** was obtained after purification by column chromatography on silica gel (EtOAc:hexane = 30:70) as a colorless solid; R_f = 0.5 (EtOAc : hexane = 1:4); yield: 80% (2.7 g); mp 82-84 ^{o}C; IR (KBr): 3382, 3061, 1670, 1513; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.54 (s, 1H), 8.36 (d, 1H, J = 4.4 Hz)), 7.59 (d, 1H, J = 7.7 Hz), 7.40-7.27 (m, 6H), 4.65 (d, 2H, J = 6.0 Hz), 2.79 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 165.9, 147.1, 145.5, 140.9, 138.6, 135.5, 128.7, 127.8, 127.4, 125.7, 43.3, 20.6.



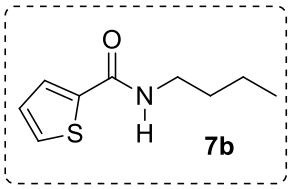
4j

***N*-Butylbenzamide (7a):** Following the general procedure, **7a** was obtained after purification by column chromatography on silica gel (EtOAc:hexane = 1:4) as colorless oil; R_f = 0.4 (EtOAc:hexane = 1:4); yield: 93% (2.45 g); IR (KBr): 3315, 2959, 1639, 1543 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.79–7.64 (m, 2H), 7.50-7.39 (m, 3H), 6.44 (br s, 1H), 3.44 (q, 2H, J = 6.8 Hz), 1.63–1.55 (m, 2H), 1.45–1.35 (m, 2H), 0.95 (t, 3H, J = 7.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 167.7, 134.8, 131.3, 128.5, 126.9, 39.8, 31.7, 20.2, 13.8; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{11}H_{16}NO$: 178.1232; found 178.1235.



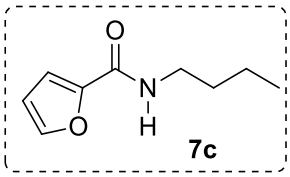
7a

***N*-Butylthiophene-2-carboxamide (7b):** Following the general procedure, **7b** was obtained after purification by column chromatography on silica gel (EtOAc:hexane = 1:4) as a colorless solid; R_f = 0.3 (EtOAc:hexane = 1:4); yield: 97% (2.66 g); IR (KBr): cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.57 (d, 1H, *J* = 3.6 Hz), 7.45 (d, 1H, *J* = 5.0 Hz), 7.06–7.03 (m, 1H), 6.57 (br s, 1H), 3.41 (q, 2H, *J* = 6.9 Hz), 1.61–1.54 (m, 2H), 1.42–1.33 (m, 2H), 0.93 (t, 3H, *J* = 7.3 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 162.1, 139.4, 129.7, 127.8, 127.6, 39.8, 31.7, 20.1, 13.8; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_9H_{14}NOS$: 184.0796; found 184.0792.



7b

***N*-Butylfuran-2-carboxamide (7c):** Following the general procedure, **7c** was obtained after purification by column chromatography on silica gel (EtOAc:hexane = 1:4) as a colorless oil; R_f = 0.3 (EtOAc:hexane = 1:4); yield: 87% (2.18 g); IR (KBr): cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.42 (d, 1H, *J* = 0.8 Hz), 7.08 (dd, 1H, J_1 = 3.5 Hz, J_2 = 0.6 Hz), 6.48–6.47 (m, 2H), 3.41 (q, 2H, *J* = 7.0 Hz), 1.61–1.53 (m, 2H), 1.43–1.34 (m, 2H), 0.94 (t, 3H, *J* = 7.3 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 158.4, 148.2, 143.7, 113.9, 112.1, 38.9, 31.7, 20.1, 13.8; MS (ESI) $C_9H_{14}NO_2$: *m/z* 168 $[M + H]^+$.

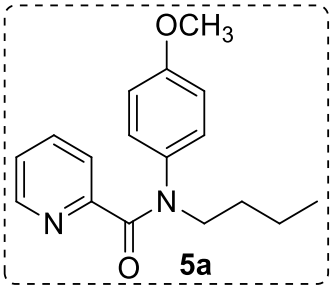


7c

General Procedure for the Ni(II)-catalyzed *N*-arylation of secondary acyclic amides (2-picolinamides) 4 with aryl halides:

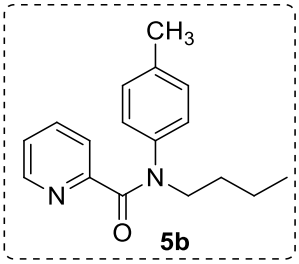
An oven dried Shlenk tube was charged with an appropriate picolinamide (0.25 mmol), $NiCl_2{\cdot}(H_2O)_6$ (10 mol%, 6.0 mg), aryl halide (4 equiv, 1 mmol), NaH (3 equiv, 0.75 mmol, 30 mg) (60 % dispersion in mineral oil) and dry DMF (3.5 mL) under a nitrogen atmosphere. Then, the reaction mixture was stirred at 150 °C for 24 h. The resulting suspension was allowed to attain the room temperature. Then, 0.3 mL of EtOH was added to quench excess of NaH and the reaction mixture was stirred at rt for 5 min and then, water (10 mL) was added to the reaction mixture. Next, the reaction mixture was transferred into a separating funnel and extracted with EtOAc (3 × 10 mL). Then, the combined organic layers were washed with saturated aqueous $NaHCO_3$, dried with anhydrous Na_2SO_4, concentrated in vacuum to afford a crude reaction mixture. Then, the crude reaction mixture was purified by silica gel column (100-200 mesh, eluent; EtOAc: hexane) to afford the corresponding *N*-arylated picolinamides.

***N*-Butyl-*N*-(4-methoxyphenyl)picolinamide (5a):** Following the general procedure, **5a** was obtained after purification by column chromatography on silica gel (EtOAc:hexane = 3:2) as a

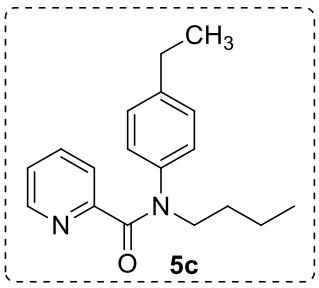


brown oil; R_f = 0.3 (EtOAc:hexane = 2:3); yield: 80% (57 mg); IR (KBr): 2958, 1649, 1511 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 8.36 (d, 1H, *J* = 4.5 Hz), 7.54 (td, 1H, J_1 = 7.7 Hz, J_2 = 1.5 Hz), 7.31 (d, 1H, *J* = 7.8 Hz), 7.08 (dd, 1H, J_1 = 6.8 Hz, J_2 = 5.0 Hz), 6.97 (d, 2H, *J* = 8.8 Hz), 6.70 (d, 2H, *J* = 8.8 Hz), 3.91 (t, 3H, *J* = 7.6 Hz), 3.73 (s, 3H), 1.65–1.58 (m, 2H), 1.43–1.34 (m, 2H), 0.92 (t, 3H, *J* = 7.3 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 168.6, 157.9, 154.9, 148.6, 136.0, 135.5, 129.0, 123.4, 123.2, 114.0, 55.3, 49.7, 29.6, 20.2, 13.9; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{17}H_{21}N_2O_2$: 285.1603; found 285.1604.

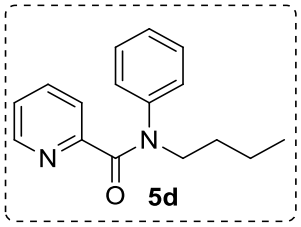
***N*-Butyl-*N*-(*p*-tolyl)picolinamide (5b):** Following the general procedure, **5b** was obtained after purification by column chromatography on silica gel (EtOAc:hexane = 1:1) as a brown oil; R_f = 0.4 (EtOAc:hexane = 2:3); yield: 75% (51 mg); IR (KBr): 2958, 1649, 1513 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 8.32 (br s, 1H), 7.5 (t, 1H, *J* = 7.4 Hz), 7.27 (d, 1H, *J* = 7.4 Hz), 7.05 (t, 1H, *J* = 5.9 Hz), 6.95 (d, 2H, *J* = 7.9 Hz), 6.89 (d, 2H, *J* = 7.9 Hz), 3.90 (t, 2H, J = 7.5 Hz), 2.2 (s, 3H), 1.62–1.55 (m, 2H), 1.39–1.30 (m, 2H), 0.90 (t, 3H, J = 7.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 168.6, 154.8, 148.6, 140.0, 136.4, 136.0, 129.5, 127.5, 123.5, 123.3, 49.7, 29.6, 20.9, 20.1, 13.9; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{17}H_{21}N_2O$: 269.1654; found 269.1651.



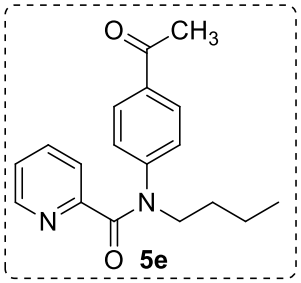
***N*-Butyl-*N*-(4-ethylphenyl)picolinamide (5c):** Following the general procedure, **5c** was obtained after purification by column chromatography on silica gel (EtOAc:hexane = 1:1) as a brown oil; R_f = 0.4 (EtOAc:hexane = 2:3); yield: 84% (71 mg); IR (KBr): 2962, 1649, 1513 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 8.30 (d, 1H, *J* = 3.8 Hz), 7.48 (t, 1H, *J* = 7.4 Hz), 7.26 (d, 1H, *J* = 7.6 Hz), 7.03 (t, 1H, *J* = 5.4 Hz), 6.96 (d, 2H, *J* = 7.8 Hz), 6.90 (d, 2H, *J* = 7.8 Hz), 3.89 (t, 2H, *J* = 7.4 Hz), 2.50 (q, 2H, *J* = 7.4 Hz), 1.62–1.55 (m, 2H), 1.38–1.29 (m, 2H), 1.11 (t, 3H, *J* = 7.5 Hz), 0.87 (t, 3H, *J* =7.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 168.5, 154.8, 148.5, 142.7, 140.2, 136.0, 128.3, 127.5, 123.5, 123.3, 49.7, 29.6, 28.2, 20.1, 15.2, 13.9; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{18}H_{23}N_2O$: 283.1810; found 283.1812.



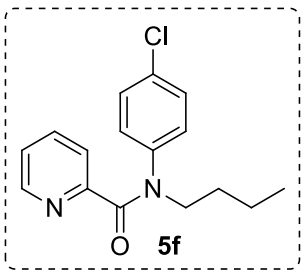
***N*-Butyl-*N*-phenylpicolinamide (5d):** Following the general procedure, **5d** was obtained after purification by column chromatography on silica gel (EtOAc:hexane = 45:55) as a yellow solid; R_f = 0.4 (EtOAc:hexane = 2:3); yield: 74% (47 mg); mp 49–51 ºC; IR (KBr): 2958, 1648, 1595 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 8.30 (br s, 1H), 7.51 (br s, 1H), 7.34 (br s, 1H), 7.16–7.03 (m, 6H), 3.93 (br s, 2H), 1.60 (br s, 2H), 1.36 (br s, 2H), 0.89 (br s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 168.5, 154.7, 148.5, 142.9, 136.1, 128.9, 127.7, 126.6, 123.7, 123.5, 49.8, 29.7, 20.2, 13.9; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{16}H_{19}N_2O$: 255.1497; found 255.1509.



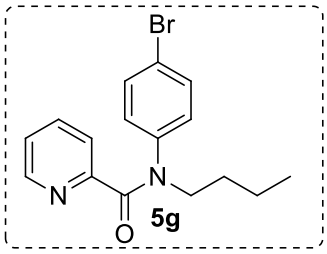
***N*-(4-Acetylphenyl)-*N*-butylpicolinamide (5e):** Following the general procedure, **5e** was obtained after purification by column chromatography on silica gel (EtOAc:hexane = 45:55) as a brown oil; R_f = 0.2 (EtOAc:hexane = 2:3); yield: 34% (26 mg); IR (KBr): 2959, 2932, 1681, 1599 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 8.31 (d, 1H, *J* = 4.0 Hz), 7.82 (d, 2H, *J* = 8.3 Hz), 7.65 (t, 1H, *J* = 7.7 Hz), 7.55 (d, 1H, *J*= 7.7 Hz), 7.18–7.12 (m, 3H), 3.99 (t, 2H, *J* = 7.6 Hz), 2.55 (s, 3H), 1.66–1.59 (m, 2H), 1.41–1.32 (m, 2H), 0.91 (t, 3H, *J* = 7.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 197.1, 168.4, 154.0, 148.4, 147.5, 136.5, 134.8, 129.2, 127.2, 124.3, 124.0, 50.0, 29.9, 26.6, 20.1, 13.8; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{18}H_{21}N_2O_2$: 297.1603; found 297.1597. The ^1H NMR signals for this amide were obtained as broad signals.



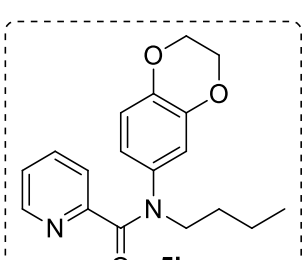
***N*-Butyl-*N*-(4-chlorophenyl)picolinamide (5f):** Following the general procedure, **5f** was obtained after purification by column chromatography on silica gel (EtOAc:hexane = 45:55) as a brown solid; R_f = 0.5 (EtOAc:hexane = 2:3); yield: 52% (38 mg); mp 85-87 ºC; IR (KBr): 2958, 1650, 1488, cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 8.33 (br s, 1H), 7.61–6.80 (m, 7H), 3.91 (br s, 2H), 1.63–1.56 (m, 2H), 1.35 (br s, 2H), 0.90 (br s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 154.2, 148.5, 138.1, 136.4, 132.1, 129.5, 129.3, 124.1, 123.7, 49.9, 29.7, 20.1, 13.8; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{16}H_{18}ClN_2O$: 289.1108; found 289.1105. The ^1H NMR signals for this amide were obtained as broad signals.



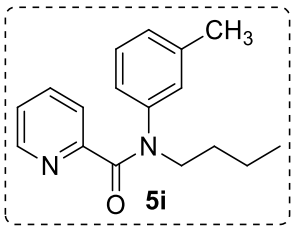
***N*-(4-Bromophenyl)-*N*-butylpicolinamide (5g):** Following the general procedure, **5g** was obtained after purification by column chromatography on silica gel (EtOAc:hexane = 45:55) as a brown solid; R_f = 0.5 (EtOAc:hexane = 2:3); yield: 50% (42 mg); mp 61-63 ºC; IR (KBr): 2959, 1650, 1492 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 8.32 (br s, 1H), 7.60 (br s, 1H), 7.45 (br s, 1H), 7.15 (br s , 3H), 6.98 (br s, 2H), 3.91 (br s, 2H), 1.63–1.56 (m, 2H), 1.37-1.35 (m, 2H), 0.90 (br s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 168.4, 154.2, 148.5, 141.5, 136.4, 132.2, 129.1, 128.9, 124.0, 123.7, 49.9, 29.7, 20.1, 13.8; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{16}H_{18}BrN_2O$: 333.0603; found 333.0622. The ^1H NMR signals for this amide were obtained as broad signals.



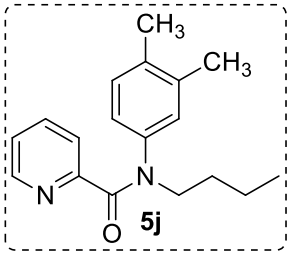
***N*-Butyl-*N*-(2,3-dihydrobenzo[*b*][1,4]dioxin-6-yl)picolinamide (5h):** Following the general procedure, **5h** was obtained after purification by column chromatography on silica gel (EtOAc:hexane = 3:2) as a brown solid; R_f = 0.3 (EtOAc:hexane = 2:3); yield: 42% (35 mg); mp 63-65 ºC; IR (KBr): 2932, 1647, 1504 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 8.39 (d, 1H, J = 4.2 Hz), 7.55 (t, 1H, J = 7.6 Hz), 7.31 (d, 1H, J = 7.7 Hz), 7.11 (t, 1H, J = 6.1Hz), 6.63-6.61 (m, 2H), 6.48 (dd, 1H, J_1 = 8.4 Hz, J_2 = 1.5 Hz), 4.18 (s, 4H), 3.88 (t, 2H, J = 7.6 Hz), 1.65–1.57 (m, 2H), 1.42–1.33 (m, 2H), 0.92 (t, 3H, J = 7.3 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 168.5, 154.8, 148.7, 143.2, 142.2, 136.1, 123.6, 123.2, 121.3, 117.1, 116.5, 64.2, 49.8, 29.6, 20.2, 13.9; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{18}H_{21}N_2O_3$: 313.1552; found 313.1519.



***N*-Butyl-*N*-(*m*-tolyl)picolinamide (5i):** Following the general procedure, **5i** was obtained after purification by column chromatography on silica gel (EtOAc:hexane = 1:1) as a brown oil; R_f = 0.5 (EtOAc:hexane = 2:3); yield: 83% (56 mg); IR (KBr): 2958, 1649, 1587 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 8.33 (br s, 1H), 7.52 (br s, 1H), 7.33 (br s, 1H), 7.07–6.79 (m, 5H), 3.93 (br s, 2H), 2.22 (s, 3H), 1.63–1.59 (m, 2H), 1.37–1.36 (m, 2H), 0.90 (br s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 168.5, 154.8, 148.5, 142.6, 138.9, 136.0, 128.6, 128.1, 127.4, 124.8, 123.6, 123.3, 49.7, 29.7, 21.2, 20.1, 13.8; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{17}H_{21}N_2O$: 269.1654; found 269.1670. The ^1H NMR signals for this amide were obtained as broad signals.

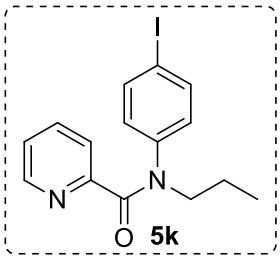


***N*-Butyl-*N*-(3,4-dimethylphenyl)picolinamide (5j):** Following the general procedure, **5j** was



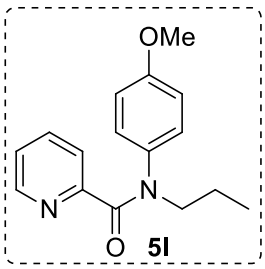
obtained after purification by column chromatography on silica gel (EtOAc:hexane = 1:1) as a brown oil; R_f = 0.5 (EtOAc:hexane = 2:3); yield: 80% (58 mg); IR (KBr): 2958, 1648, 1503 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 8.34 (br s, 1H), 7.51 (t, 1H, *J* = 6.3 Hz), 7.29 (d, 1H, *J* = 5.4 Hz), 7.06 (br s, 1H), 6.89–6.84 (m, 2H), 6.70 (d, 1H, *J* = 7.1 Hz), 3.91 (t, 2H, *J* = 7.1 Hz), 2.13 (s, 3H), 2.11 (s, 3H), 1.64–1.57 (m, 2H), 1.42–1.34 (m, 2H), 0.91 (t, 3H, *J* = 6.9 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 168.6, 155.0, 148.6, 140.2, 137.3, 136.0, 135.1, 129.9, 128.5, 125.2, 123.5, 123.3, 49.7, 29.6, 20.2, 19.7, 19.3, 13.9; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{18}H_{23}N_2O$: 283.1810; found 283.1771.

***N*-(4-Iodophenyl)-*N*-propylpicolinamide (5k):** Following the general procedure, **5k** was



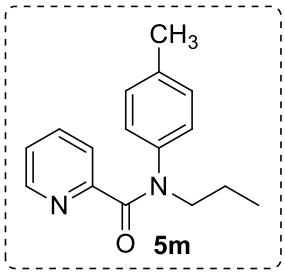
obtained after purification by column chromatography on silica gel (EtOAc:hexane = 1:1) as a brown solid; R_f = 0.5 (EtOAc:hexane = 2:3); yield: 38% (35 mg); mp 87-89 ºC; IR (KBr): 2963, 1648, 1486 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 8.35 (br s, 1H), 7.63–7.48 (m, 4H), 7.18–7.15 (m, 1H), 6.81 (br s, 2H), 3.89 (t, 2H, *J* = 6.8 Hz), 1.70–1.60 (m, 2H), 0.94 (br s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 168.3, 154.2, 148.5, 138.1, 136.4, 129.5, 127.7, 124.1, 123.7, 91.5, 51.6, 20.9, 11.3; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{15}H_{16}IN_2O$: 367.0307; found 367.0322. The ^1H NMR signals for this amide were obtained as broad signals. ^{13}C NMR of this compound contains residual grease peaks.

***N*-(4-Methoxyphenyl)-*N*-propylpicolinamide (5l):** Following the general procedure, **5l** was

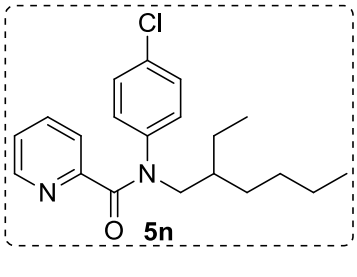


obtained after purification by column chromatography on silica gel (EtOAc:hexane = 3:2) as a brown oil; R_f = 0.2 (EtOAc:hexane = 2:3); yield: 70% (36 mg); IR (KBr): 2964, 1647, 1511 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 8.35 (d, 1H, *J* = 3.6 Hz), 7.52 (t, 1H, *J* = 7.6 Hz), 7.29 (d, 1H, *J* = 7.6 Hz), 7.08 (t, 1H, *J* = 5.3 Hz), 6.97 (d, 2H, *J* = 8.2 Hz), 6.69 (d, 2H, *J* = 8.2 Hz), 3.87 (t, 2H, *J* = 7.4 Hz), 3.71 (s, 3H), 1.69–1.60 (m, 2H), 0.95 (t, 3H, *J* = 7.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 168.7, 158.0, 154.9, 148.6, 136.0, 135.4, 129.0, 123.4, 123.2, 114.0, 55.3, 51.5, 20.7, 11.3; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{16}H_{19}N_2O_2$: 271.1447; found 271.1415.

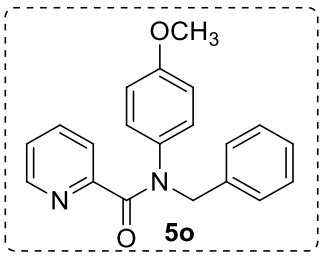
***N*-Propyl-*N*-(*p*-tolyl)picolinamide (5m):** Following the general procedure, **5m** was obtained after purification by column chromatography on silica gel (EtOAc:hexane = 1:1) as a yellow solid; R_f = 0.4 (EtOAc:hexane = 2:3); yield: 90% (57 mg); mp 87-89 °C; IR (KBr): 2963, 1648, 1512 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 8.38 (d, 1H, *J* = 3.4 Hz), 7.55 (t, 1H, *J* = 7.4 Hz), 7.33 (d, 1H, *J* = 7.6 Hz), 7.11 (t, 1H, *J* = 5.1 Hz), 6.99 (d, 2H, *J* = 7.5 Hz), 6.94 (d, 2H, *J* = 7.5 Hz), 3.91 (t, 2H, *J* = 7.4 Hz), 2.26 (s, 3H), 1.70-1.64 (m, 2H), 0.97 (t, 3H, *J* = 7.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 168.6, 154.9, 148.6, 140.1, 136.4, 136.0, 129.5, 127.5, 123.5, 123.3, 51.5, 21.0, 20.7, 11.3; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{16}H_{19}N_2O$: 255.1497; found 255.1500.



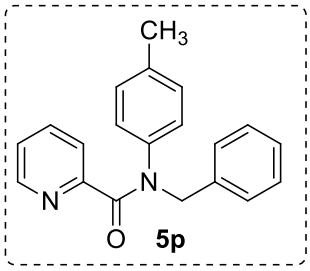
***N*-Propyl-*N*-(*p*-tolyl)picolinamide (5n):** Following the general procedure described above, **5n** was obtained after purification by column chromatography on silica gel (EtOAc:hexane = 45:55) as a brown solid; R_f = 0.3 (EtOAc:hexane = 2:3); yield: 44% (38 mg); mp 48-50 °C; IR (KBr): 2958, 2928, 2859, 1653, 1492 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 8.33 (br s, 1H), 7.60–6.99 (m, 7H), 3.94–3.82 (m, 2H), 1.55–1.24 (m, 9H), 0.87 (t, 6H, *J* = 6.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 168.8, 154.5, 148.4, 141.5, 136.3, 132.1, 129.0, 128.8, 123.8, 123.6, 52.6, 37.3, 30.3, 28.5, 23.6, 23.0, 14.1, 10.5; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{20}H_{26}ClN_2O$: 345.1734; found 345.1739. The ^1H NMR signals for this amide were obtained as broad signals.



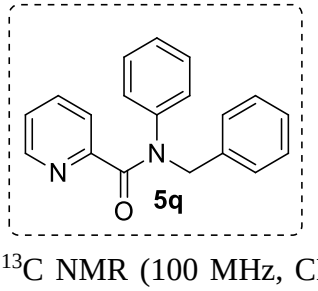
***N*-Benzyl-*N*-(4-methoxyphenyl)picolinamide (5o):** Following the general procedure, **5o** was obtained after purification by column chromatography on silica gel (EtOAc:hexane = 3:2) as a brown oil; R_f = 0.3 (EtOAc:hexane = 2:3); yield: 95% (76 mg); IR (KBr): 2934, 1649, 1511 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 8.38 (d, 1H, *J* = 4.3 Hz), 7.55 (t, 1H, *J* = 7.6 Hz), 7.37–7.25 (m, 6H), 7.10 (t, 1H, *J* = 5.5 Hz), 6.83 (d, 2H, *J* = 8.7 Hz), 6.61 (d, 2H, *J* = 8.7 Hz), 5.11 (s, 2H), 3.68 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 168.9, 158.0, 154.6, 148.7, 137.1, 136.1, 135.3, 129.1, 128.8, 128.5, 127.4, 123.6, 123.4, 113.9, 55.3, 53.6; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{20}H_{19}N_2O_2$: 319.1447; found 319.1447.



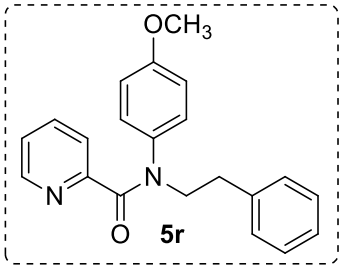
***N*-Benzyl-*N*-(*p*-tolyl)picolinamide (5p):** Following the general procedure, **5p** was obtained after purification by column chromatography on silica gel (EtOAc:hexane = 1:1) as a pale yellow solid; R_f = 0.4 (EtOAc:hexane = 2:3); yield: 81% (61 mg); mp 110-112 °C; IR (KBr): 3030, 1650, 1512 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 8.38 (s, 1H), 7.55 (t, 1H, *J* = 6.8 Hz), 7.39–7.23 (m, 6H), 7.11 (br s, 1H), 6.90 (d, 2H, *J* = 7.0 Hz), 6.81 (d, 2H, *J* = 7.0 Hz), 5.14 (s, 2H), 2.21 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 168.8, 154.4, 148.6, 140.0, 137.1, 136.5, 136.1, 129.5, 128.6, 128.5, 127.5, 127.4, 123.7, 123.5, 53.5, 21.0; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{20}H_{19}N_2O$: 303.1497; found 303.1518.



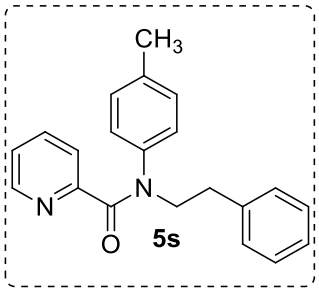
***N*-Benzyl-*N*-phenylpicolinamide (5q):** Following the general procedure, **5q** was obtained after purification by column chromatography on silica gel (EtOAc:hexane = 45:65) as slight yellow solid; R_f = 0.4 (EtOAc:hexane = 2:3); yield: 65% (46 mg); mp 91-93 °C; IR (KBr): 2928, 1649, 1595 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 8.36 (br s, 1H), 7.59–7.56 (m, 1H), 7.45–7.44 (m, 1H), 7.35–7.23 (m, 5H), 7.13–7.10 (m, 1H), 6.95–6.94 (m, 1H), 5.18 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 168.8, 154.4, 148.6, 142.8, 137.1, 136.1, 128.8, 128.5, 128.5, 127.7, 127.4, 126.7, 123.9, 123.7, 53.6; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{19}H_{17}N_2O$: 289.1341; found 289.1346. The ^1H NMR signals for this amide were obtained as broad signals.



***N*-(4-Methoxyphenyl)-*N*-phenethylpicolinamide (5r):** Following the general procedure, **5r** was obtained after purification by column chromatography on silica gel (EtOAc:hexane = 3:2) as a pale yellow solid; R_f = 0.2 (EtOAc:hexane = 2:3); yield: 86% (71 mg); mp 121-123 °C; IR (KBr): 2933, 1647, 1511 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 8.38 (d, 1H, *J* = 4.5 Hz), 7.57–7.53 (m, 1H), 7.33–7.22 (m, 6H), 7.12-7.09 (m, 1H), 6.90 (d, 2H, *J* = 8.8 Hz), 6.70 (d, 2H, *J* = 8.8 Hz), 4.15–4.11 (m, 2H), 3.74 (s, 3H), 3.03 (t, 2H, *J* = 8.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 168.7, 158.0, 154.7, 148.7, 138.9, 136.0, 135.6, 129.0, 128.9, 128.5, 126.4, 123.6, 123.3, 114.1, 55.3, 51.9, 33.7; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{21}H_{21}N_2O_2$: 333.1603; found 333.1608.

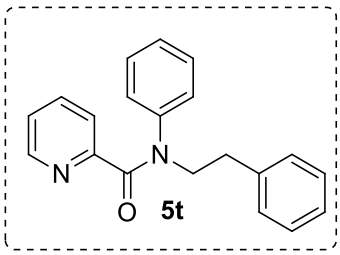


***N*-Phenethyl-*N*-(*p*-tolyl)picolinamide (5s):** Following the general procedure, **5s** was obtained



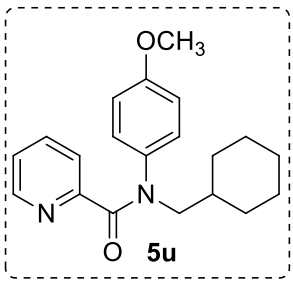
after purification by column chromatography on silica gel (EtOAc:hexane = 1:1) as a pale yellow solid; R_f = 0.4 (EtOAc:hexane = 2:3); yield: 82% (65 mg); mp 101-103 ºC; IR (KBr): 2963, 1649, 1513 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 8.39 (d, 1H, *J* = 3.1 Hz), 7.56 (t, 1H, *J* = 7.3 Hz), 7.36–7.21 (m, 6H), 7.13 (t, 1H, *J* = 5.0 Hz), 6.99 (d, 2H, *J* = 7.5 Hz), 6.87 (d, 2H, *J* = 7.5 Hz), 4.15 (t, 2H, *J* = 8.1 Hz), 3.03 (t, 2H, *J* = 8.1 Hz), 2.27 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 168.6, 154.6, 148.7, 140.3, 138.9, 136.5, 136.1, 129.6, 129.0, 128.5, 127.4, 126.4, 123.7, 123.5, 51.9, 33.7, 21.0; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{21}H_{21}N_2O$: 317.1654; found 317.1668.

***N*-Phenethyl-*N*-phenylpicolinamide (5t):** Following the general procedure, **5t** was obtained after purification by column chromatography on silica gel (EtOAc:hexane = 45:65) as a pale yellow



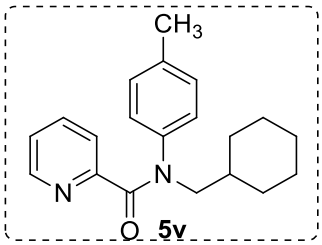
solid; R_f = 0.4 (EtOAc:hexane = 2:3); yield: 92% (70 mg); mp 81-83 ºC; IR (KBr): 2932, 1647, 1594 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 8.36 (d, 1H, *J* = 1.9 Hz), 7.56 (br s, 1H), 7.40 (d, 1H, *J* = 6.6 Hz), 7.30–7.13 (m, 11H), 6.99 (br s, 2H), 7.39-7.38 (m, 1H), 7.30–7.13 (m, 9H), 7.00-6.98 (m, 2H), 4.18 (t, 2H, *J* = 7.9 Hz), 3.04 (t, 2H, *J* = 7.9 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 168.6, 154.4, 148.6, 143.0, 138.8, 136.1, 129.0, 128.9, 128.5, 127.6, 126.7, 126.4, 123.8, 123.6, 52.0, 33.8; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{20}H_{19}N_2O$: 303.1497; found 303.1500. The ^1H NMR signals for this amide were obtained as broad signals.

***N*-(Cyclohexylmethyl)-*N*-(4-methoxyphenyl)picolinamide (5u):** Following the general



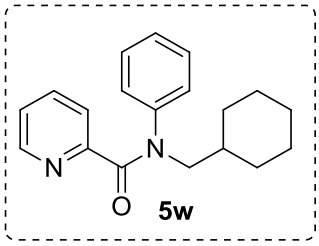
procedure, **5u** was obtained after purification by column chromatography on silica gel (EtOAc:hexane = 3:2) as a brown oil; R_f = 0.3 (EtOAc:hexane = 3:2); yield: 80% (65 mg); IR (KBr): 2925, 1649, 1511 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 8.36 (d, 1H, *J* = 4.6 Hz), 7.52 (td, 1H, J_1 = 7.7 Hz, J_2 = 1.5 Hz), 7.26 (d, 1H, *J* = 7.8 Hz), 7.08–7.05 (m, 1H), 6.97 (d, 2H, *J* = 8.8 Hz), 6.68 (d, 2H, *J* = 8.8 Hz), 3.79 (d, 2H, *J* = 7.4 Hz), 3.72 (s, 3H), 1.79–1.62 (m, 6H), 1.17–1.07 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.1, 157.8, 155.2, 148.6, 136.0, 135.8, 128.9, 123.3, 123.1, 114.0, 55.5, 55.3, 36.1, 30.8, 26.4, 26.0; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{20}H_{25}N_2O_2$: 325.1916; found 325.1937.

***N*-(Cyclohexylmethyl)-*N*-(*p*-tolyl)picolinamide (5v):** Following the general procedure, **5v** was



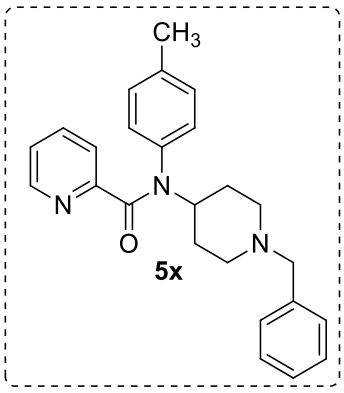
obtained after purification by column chromatography on silica gel (EtOAc:hexane = 1:1) as a yellow solid; R_f = 0.5 (EtOAc:hexane = 2:3); yield: 83% (64 mg); mp 72-74 ºC; IR (KBr): 2925, 1650, 1512 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 8.36 (d, 1H, *J* = 3.5 Hz), 7.52 (t, 1H, *J* = 7.3 Hz), 7.28 (d, 1H, *J* = 7.0 Hz), 7.08 (t, 1H, *J* = 5.2 Hz), 6.97 (d, 2H, *J* = 7.7 Hz), 6.92 (d, 2H, *J* = 7.7 Hz), 3.83 (d, 2H, *J* = 7.3 Hz), 2.24 (s, 3H), 1.79–1.63 (m, 6H), 1.16–1.06 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.0, 155.1, 148.6, 140.4, 136.3, 135.9, 129.5, 127.4, 123.4, 123.2, 55.4, 36.2, 30.8, 26.4, 25.8, 21.0; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{20}H_{25}N_2O$: 309.1967; found 309.1956.

***N*-(Cyclohexylmethyl)-*N*-phenylpicolinamide (5w):** Following the general procedure, **5w** was



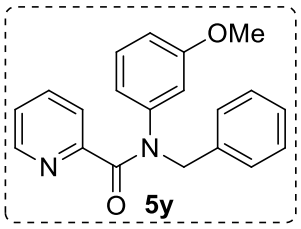
obtained after purification by column chromatography on silica gel (EtOAc:hexane = 45:55) as a yellow solid; R_f = 0.5 (EtOAc:hexane = 2:3); yield: 81% (59 mg); mp 111-113 ºC; IR (KBr): 2924, 1649, 1594 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 8.36 (br s, 1H), 7.56-7.54 (m, 1H) 7.34–7.07 (m, 7H), 3.85 (d, 2H, *J* = 6.9 Hz), 1.79–1.63 (m, 6H, 1.17-1.07 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 168.2, 154.2, 147.9, 142.9, 136.9, 129.0, 127.7, 126.7, 123.8, 123.6, 55.6, 36.2, 30.8, 26.4, 25.8; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{19}H_{23}N_2O$: 295.1810; found 295.1821.

***N*-(1-Benzylpiperidin-4-yl)-*N*-(*p*-tolyl)picolinamide (5x):** Following the general procedure, **5x**

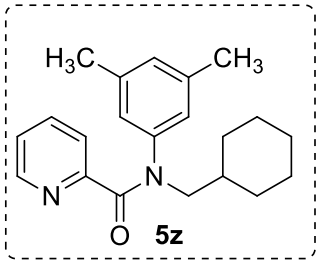


was obtained after purification by column chromatography on alumina gel (EtOAc:hexane = 4:1) as brown solid; R_f = 0.2 (EtOAc:hexane = 2:3); yield: 40% (39 mg); mp 91-93 ºC; IR (KBr): 2936, 1648, 1512 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 8.33 (d, 1H, *J* = 4.4 Hz), 7.50 (t, 1H, *J* = 7.0 Hz), 7.31–7.22 (m, 6H), 7.04 (dd, 1H, J_1 = 6.8 Hz, J_2 = 5.2 Hz), 6.96 (d, 2H, *J* = 8.2 Hz), 6.92 (d, 2H, *J* = 8.2 Hz), 4.82–4.76 (m, 1H), 3.48 (s, 2H), 2.95 (d, 2H, *J* = 11.4 Hz), 2.23 (s, 3H), 2.23-2.17 (m, 2H), 1.95–1.91 (m, 2H), 1.63–1.53 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.0, 155.3, 148.5, 138.2, 137.4, 135.9, 130.7, 129.2, 129.1, 128.2, 127.0, 123.2, 122.9, 63.0, 53.4, 53.0, 30.3, 21.0; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{25}H_{28}N_3O$: 386.2232; found 386.2231.

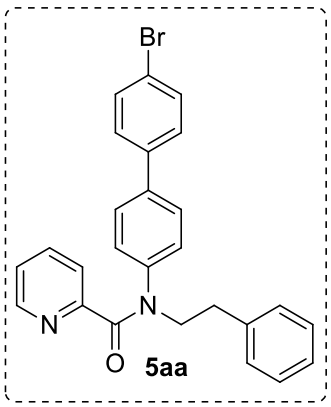
***N*-Benzyl-*N*-(3-methoxyphenyl)picolinamide (5y):** Following the general procedure, **5y** was obtained after purification by column chromatography on silica gel (EtOAc:hexane = 3:2) as brown solid; R_f = 0.3 (EtOAc:hexane = 2:3); yield: 75% (60 mg); mp 61-63 °C; IR (KBr): 2937, 1652, 1601 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 8.41 (br s, 1H), 7.59 (t, 1H, *J* = 7.0 Hz), 7.44–7.15 (m, 7H), 7.02 (t, 1H, *J* = 7.5 Hz), 6.64–6.48 (m, 3H), 5.16 (s, 2H), 3.60 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 168.8, 159.8, 154.4, 148.7, 143.8, 137.2, 136.2, 129.4, 128.5, 128.4, 127.4, 123.9, 123.5, 119.9, 113.3, 112.6, 55.2, 53.5; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{20}H_{19}N_2O_2$: 319.1447; found 319.1458. The ^1H NMR signals for this amide were obtained as broad signals.



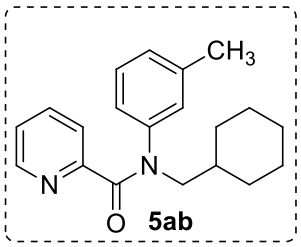
***N*-(Cyclohexylmethyl)-*N*-(3,5-dimethylphenyl)picolinamide (5z):** Following the general procedure, **5z** was obtained after purification by column chromatography on silica gel (EtOAc:hexane = 45:55) as a yellow solid; R_f = 0.7 (EtOAc:hexane = 2:3); yield: 78% (63 mg); mp 86-88 °C; IR (KBr): 2924, 1651, 1594 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 8.37 (br s, 1H), 7.51 (br s, 1H), 7.27 (d, 1H, *J* = 6.6 Hz), 7.08 (br s, 1H), 6.71-6.64 (m, 3H), 3.82 (d, 2H, *J* = 6.7 Hz), 2.16 (s, 6H), 1.78–1.1.62 (m, 6H), 1.17-1.06 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.0, 155.2, 148.5, 142.8, 138.4, 135.9, 128.2, 125.2, 123.4, 123.2, 55.3, 36.2, 30.8, 26.4, 25.8, 21.1; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{21}H_{27}N_2O$: 323.2123; found 323.2126. The ^1H NMR signals for this amide were obtained as broad signals.



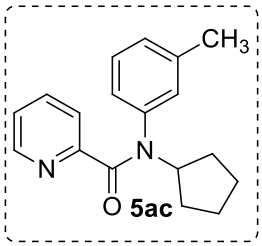
***N*-(4'-Bromo-[1,1'-biphenyl]-4-yl)-*N*-phenethylpicolinamide (5aa):** Following the general procedure, **5aa** was obtained after purification by column chromatography on silica gel (EtOAc:hexane = 45:55) as brown solid; R_f = 0.5 (EtOAc:hexane = 2:3); yield: 58% (66 mg); mp 136-138 °C; IR (KBr): 2932, 1648, 1483 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 8.37 (br s, 1H), 7.62–7.03 (m, 16H), 4.21 (br s, 2H), 3.07 (t, 2H, *J* = 7.1 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 168.5, 154.3, 148.6, 138.7, 136.3, 131.9, 129.0, 128.8, 128.5, 127.9, 127.8, 127.6, 127.4, 127.3, 126.9, 126.5, 123.8, 121.8, 52.1, 33.9; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{26}H_{22}BrN_2O$: 457.0916; found 457.0931. The ^1H NMR signals for this amide were obtained as broad signals.



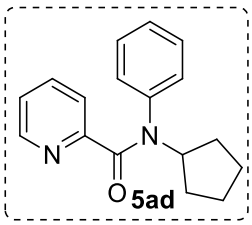
***N*-(Cyclohexylmethyl)-*N*-(*m*-tolyl)picolinamide (5ab):** Following the general procedure, **5ab** was obtained after purification by column chromatography on silica gel (EtOAc:hexane = 45:55) as a yellow solid; R_f = 0.7 (EtOAc:hexane = 2:3); yield: 65% (49 mg); mp 88-90 °C; IR (KBr): 2924, 1651, 1587 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 8.37 (br s, 1H), 7.54–7.53 (m, 1H), 7.31–7.28 (m, 1H), 7.09–6.80 (m, 5H), 3.84 (d, 2H, *J* = 6.3 Hz), 2.20 (s, 3H), 1.79–1.64 (m, 6H), 1.20–1.10 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.0, 155.0, 148.5, 143.0, 138.8, 136.0, 128.5, 128.0, 127.3, 124.8, 123.5, 123.3, 55.4, 36.2, 30.8, 26.4, 25.8, 21.2; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{20}H_{25}N_2O$: 309.1967; found 309.1971. The ^1H NMR signals for this amide were obtained as broad signals.



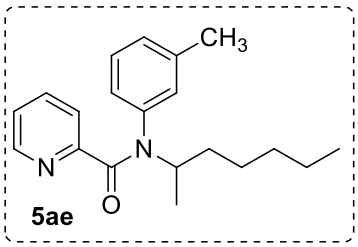
***N*-Cyclopentyl-*N*-(*m*-tolyl)picolinamide (5ac):** Following the general procedure, **5ac** was obtained after purification by column chromatography on silica gel (EtOAc:hexane = 45:55) as a pale yellow solid; R_f = 0.5 (EtOAc:hexane = 2:3); yield: 52% (36 mg); mp 67-69 °C; IR (KBr): 2957, 1648, 1586 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 8.34 (br s, 1H), 7.52–7.50 (m, 1H), 7.28–7.26 (m, 1H), 7.06–6.88 (m, 1H), 5.04-5.02 (m, 1H), 2.24 (s, 3H), 2.02 (br s, 2H), 1.58–1.48 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.2, 155.4, 148.5, 139.2, 138.4, 135.9, 131.3, 128.2, 127.8, 123.2, 123.2, 122.9, 58.0, 29.5, 22.9, 21.2; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{18}H_{21}N_2O$: 281.1654; found 281.1656. The ^1H NMR signals for this amide were obtained as broad signals.



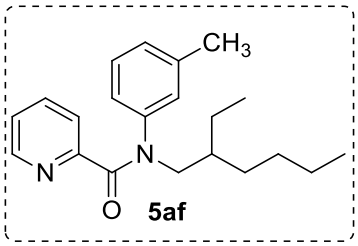
***N*-Cyclopentyl-*N*-phenylpicolinamide (5ad):** Following the general procedure, **5ad** was obtained after purification by column chromatography on silica gel (EtOAc:hexane = 45:55) as a pale yellow solid; R_f = 0.5 (EtOAc:hexane = 2:3); yield: 68% (45 mg); mp 111-113 °C; IR (KBr): 2959, 1642, 1493 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 8.31 (br s, 1H), 7.51-7.49 (br s, 1H), 7.28–7.04 (m, 7H), 5.06-5.04 (m, 1H), 2.02 (br s, 2H), 1.57–1.46 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.2, 155.3, 148.5, 139.3, 136.0, 130.8, 128.5, 127.5, 123.3, 123.0, 58.0, 29.5, 23.0; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{17}H_{19}N_2O$: 267.1497; found 267.1504. The ^1H NMR signals for this amide were obtained as broad signals.



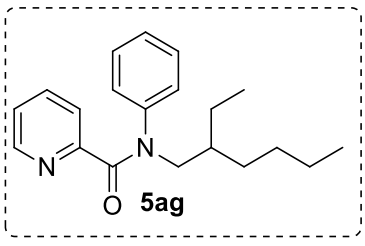
***N*-(Heptan-2-yl)-*N*-(*m*-tolyl)picolinamide (5ae):** Following the general procedure, **5ae** was obtained after purification by column chromatography on silica gel (EtOAc:hexane = 45:55) as a yellow oil; R_f = 0.6 (EtOAc:hexane = 2:3); yield: 52% (40 mg); IR (KBr): 2956, 1648, 1586 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 8.33 (d, 1H, *J* = 4.1 Hz), 7.49 (t, 1H, *J* = 7.5 Hz), 7.24 (d, 1H, *J* = 7.7 Hz), 7.05–6.83 (m, 5H), 4.97-4.92 (m, 1H), 2.22 (s, 3H), 1.75–1.67 (m, 1H), 1.47–1.32 (m, 7H), 1.22 (d, 3H, *J* = 6.8 Hz), 0.90 (t, 3H, *J* = 6.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 168.9, 155.5, 148.5, 139.2, 138.3, 135.8, 130.9, 128.1, 128.0, 127.4, 123.1, 122.9, 52.1, 35.0, 31.8, 26.5, 22.6, 21.2, 19.1, 14.1; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{20}H_{27}N_2O$: 311.2123; found 311.2128.



***N*-(2-Ethylhexyl)-*N*-(*m*-tolyl)picolinamide (5af):** Following the general procedure, **5af** was obtained after purification by column chromatography on silica gel (EtOAc:hexane = 45:55) as a yellow oil; R_f = 0.6 (EtOAc:hexane = 2:3); yield: 67% (54 mg); IR (KBr): 2958, 1651, 1605 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 8.36 (br s, 1H), 7.54-7.52 (m, 1H), 7.30-7.28 (m, 1H), 7.09–6.80 (m, 5H), 3.97–3.84 (m, 2H), 2.22 (s, 3H), 1.59–1.23 (m, 9H), 0.86 (br s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.0, 155.1, 148.5, 142.6, 138.8, 135.9, 128.5, 128.0, 127.3, 124.7, 123.5, 123.3, 52.4, 37.3, 30.3, 28.5, 23.6, 23.0, 21.2, 14.1, 10.5; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{21}H_{29}N_2O$: 325.2280; found 325.2296. The ^1H NMR signals for this amide were obtained as broad signals.

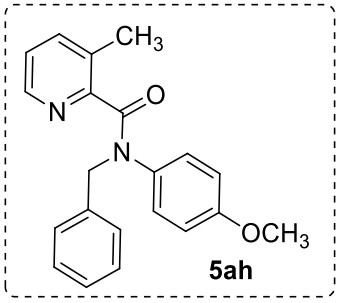


***N*-(2-Ethylhexyl)-*N*-phenylpicolinamide (5ag):** Following the general procedure, **5ag** was obtained after purification by column chromatography on silica gel (EtOAc:hexane = 45:55) as yellow oil; R_f = 0.6 (EtOAc:hexane = 2:3); yield: 56% (43 mg); IR (KBr): 2958, 1650, 1595 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 8.34 (br s, 1H), 7.55-7.52 (m, 1H), 7.33–7.7.31 (m, 1H), 7.18–7.05 (m, 6H), 4.02–3.86 (m, 2H), 1.59–1.23 (m, 9H), 0.86 (t, 6H, *J* = 6.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.0, 155.0, 148.5, 142.8, 136.0, 128.8, 127.6, 126.5, 123.5, 123.4, 52.5, 37.4, 30.3, 28.5, 23.7, 23.0, 14.1, 10.5; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{20}H_{27}N_2O$: 311.2123; found 311.2130.

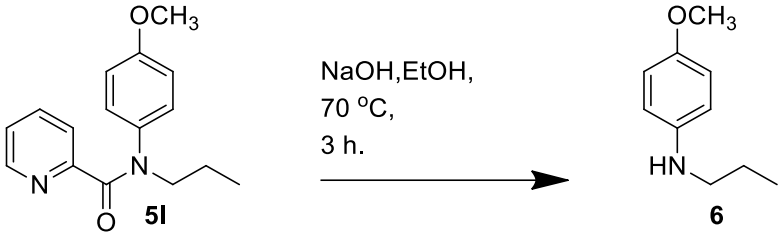


***N*-Benzyl-*N*-(4-methoxyphenyl)-3-methylpicolinamide (5ah):** Following the general procedure, **5ah** was obtained after purification by column chromatography on silica gel (EtOAc:

hexane = 55:45) as a yellow oil; R_f = 0.3 (EtOAc:hexane = 2:3); yield: 41% (34 mg); IR (KBr): 3061, 2933, 1649, 1511; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.24 (d, 1H, J = 4.5 Hz)), 7.37-7.27 (m, 6H), 6.99 (dd, 1H, J_1=7.8 Hz, J_2=4.8 Hz), 6.87 (d, 2H, J = 9.0 Hz), 6.60 (d, 2H, J = 9.0 Hz), 5.11 (s, 2H), 3.66 (s, 3H), 2.31 (s, 3H) ; ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.0, 158.2, 154.6, 146.1, 137.8, 137.2, 134.0, 129.8, 129.2, 128.9, 128.5, 127.5, 123.1, 113.7, 55.2, 52.8, 17.9.



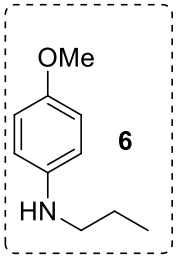
5ah



5l **6**

Procedure for hydrolysis of 3l and preparation of 4-methoxy-*N*-propylaniline (6): To round bottom flask *N*-(4-methoxyphenyl*)*-*N*-propylpicolinamide (**5l**, 68 mg, 0.25 mmol), NaOH (80 mg, 2 mmol) and ethanol (3 mL) were added. The mixture was refluxed at 70 °C for 3-5 h. Then, water (5 mL) was added and extracted with diethyl ether (3 × 10 mL). The resulting organic layer was dried with anhydrous Na_2SO_4 and the solvent was removed under reduced pressure. The residue was purified by column chromatography on silica gel to give the pure product **6**.

4-Methoxy-*N*-propylaniline (6): Following the general procedure, **6** was obtained after purification by column chromatography on silica gel (EtOAc:hexane = 45:55) as a brown oil; R_f = 0.9 (EtOAc:hexane = 2:3); yield: 76% (31 mg); IR (KBr): 2932, 1599, 1513 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.82 (dt, 2H, J_1 = 8.9 Hz, J_2 = 3.6 Hz), 6.61 (dt, 2H, J_1 = 8.9 Hz, J_2 = 3.6 Hz), 3.78 (s, 3H), 3.07 (t, 2H, J = 7.1 Hz), 1.70–1.61 (m, 2H), 1.03 (t, 3H, J = 7.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 152.0, 142.9, 114.9, 114.0, 55.8, 46.9, 22.8, 11.7; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{10}H_{16}NO$: 166.1232; found 166.1226.



6

References

1) a) Cogo, J.; Kaplum, V.; Sangi, D. P.; Ueda-Nakamura, T.; Correa, A. G.; Nakamura, C. V. *Eur. J. Med. Chem.* **2015**, *90*, 107. b) Harjivan, S. G.; Wanke, R.; Silva, J. L. F.; Marques, M. M.; Antunes, A. M. M. *Eur. J. Med. Chem.* **2014**, *74*, 7. c) Liu, K.; Chen, W.; Zhan, P.; Clercq, E. D.;

Pannecouque, C.; Liu, X. *Eur. J. Med. Chem.* **2014**, *87*, 52. d) Stoli, I.; Paljetak, H. C.; Peri, M.; Matija, M.; Stepani, V.; Verbanac, D.; Baji, M. *Eur. J. Med. Chem.* **2015**, *90*, 68.

2) a) Vitaku, E.; Smith, D. T.; Njardarson, J. T. *J. Med. Chem.* **2014**, *57*, 10257. b) Vasilenko, V.; Roth, T.; Blasius, C. K.; Intorp, S. P.; Wadepohl, H.; Gade, L. H. *Beilstein J. Org. Chem.* **2016**, *12*, 846. c) Tasler, S.; Mies, J.; Lang, M. *Adv. Synth. Catal.* **2007**, *349*, 2286. d) Roughley, S. D.; Jordan, A. M. *J. Med. Chem.* **2011**, *54*, 3451. e) Magano, J.; Dunetz, J. R. *Chem. Rev.* **2011**, *111*, 2177. f) Buchwald, S. L.; Mauger, C.; Mignani, G.; Scholz, U. *Adv. Synth. Catal.* **2006**, *348*, 23. g) Carey, J. S.; Laffan, D.; Thomson, C.; Williams, M. T. *Org. Biomol. Chem.* **2006**, *4*, 2337. h) Tai, S.; Dover, E. J.; Marchi, S. V.; Carrick, J. D. *J. Org. Chem.* **2015**, *80*, 6275. i) Alayrac, C.; Schollmeyer, D.; Witulski, B. *Chem. Commun.* **2009**, *12*, 1464.

3) a) Semmelhack, M. F.; Rhee, H. *Tetrahedron Lett*. **1993**, *34*, 1395. b) Hattori, T.; Sakamoto, J.; Hayashizaka, N.; Miyano, S. *Synthesis*, **1994**, 199. c) Bunnett, J. F. *Acc. Chem. Res.*, **1978**, *11*, 413. d) Chen, J.; Huang, D.; Ding, Y. *Tetrahedron Lett*, **2017**, *58*, 4240.

4) a) Falk, F. C.; Frohlich, R.; Paradies, J. *Chem. Commun.* **2011**, *47*, 11095. b) Wolfe, J. P.; Rennels, R. A.; Buchwald, S. L. *Tetrahedron* **1996**, *52*, 7525. c) Yin, J.; Buchwald, S. L. *Org. Lett.* **2000**, *2*, 1101. d) Crawford, S. M. Lavery, C. B.; Stradiotto, M. *Chem. Eur. J.* **2013**, *19*, 16760. e) Shen, Q.; Shekhar, S.; Stambuli, J. P.; Hartwig, J. F. *Angew. Chem., Int. Ed.* **2005**, *44*, 1371. f) Ma, F.; Xie, X.; Zhang, L.; Peng, Z.; Ding, L.; Fu, L.; Zhang, Z. *J. Org. Chem.* **2012**, *77*, 5279. g) Falk, F. C.; Frohlich, R.; Paradies, J. *Chem. Commun.* **2011**, *47*, 11095.

5) a) Ghosh, A.; Sieser, J. E.; Riou, M.; Cai, W.; Rivera-Ruiz, L. *Org. Lett.* **2003**, *5*, 2207. b) Hicks, J. D.; Hyde, A. M.; Cuezva, A. M.; Buchwald, S. L. *J. Am. Chem. Soc.* **2009**, *131*, 16720. c) Yang, B. H.; Buchwald, S. L. *Org. Lett.* **1999**, *1*, 35.

6) a) Ruiz-Castillo, P.; Buchwald, S. L. *Chem. Rev.* **2016**, *116*, 12564. b) Beletskaya, I. P.; Cheprakov, A. V. *Coord. Chem. Rev.* **2004**, *248*, 2337.

7) a) Peifer, C.; Urich, R.; Schattel, V.; Abadleh, M.; Röttig, M.; Kohlbacher, O.; Laufer, S. *Bioorg. Med. Chem. Lett.* **2008**, *18*, 1431. b) Liang, J.; van Abbema, A.; Balazs, M.; Barrett, K.; Berezhkovsky, L.; Blair, W.; Chang, C.; Delarosa, D.; DeVoss, J.; Driscoll, J.; Eigenbrot, C.; Ghilardi, N.; Gibbons, P.; Halladay, J.; Johnson, A.; Kohli, P. B.; Lai, Y.; Liu, Y.; Lyssikatos, J.; Mantik, P.; Menghrajani, K.; Murray, J.; Peng, I.; Sambrone, A.; Shia, S.; Shin, Y.; Smith, J.; Sohn, S.; Tsui, V.; Ultsch, M.; Wu, L. C.; Xiao, Y.; Yang, W.; Young, J.; Zhang, B.; Zhu, B.; Magnuson, S. *J. Med. Chem.* **2013**, *56*, 4521. c) Alayrac, C.; Schollmeyer, D.; Witulski, B. *Chem.*

Commun. **2009**, *12*, 1464. d) Wentzel, M. T.; Hewgley, J. B.; Kamble, R. M.; Wall, P. D.; Kozlowski, M. C. *Adv. Synth. Catal.* **2009**, *351*, 931. e) Kelly, S. M.; Han, C.; Tung, L.; Gosselin, F. *Org. Lett.* **2017**, *19*, 3021. f) Bair, J. S.; Palchaudhuri, R.; Hergenrother, P. J. *J. Am. Chem. Soc.* **2010**, *132*, 5469. g) Ganton, M. D.; Kerr, M. A. *J. Org. Chem.* **2007**, *72*, 574. h) Xue, T.; Ding, S.; Guo, B.; Zhou, Y.; Sun, P.; Wang, H.; Chu, W.; Gong, G.; Wang, Y.; Chen, X.; Yang, Y. *J. Med. Chem.* **2014**, *57*, 7770. i) Adnan, M. M. M.; Robert, A. C.; Xio-Chuan, G.; Peter, C. D.; Devi Reddy, G.; Guoxiang, H.; Robert, R.; Sameer, T.; Tripura, Y.; Christopher, B. *PCT Int. Appl.* **2005**, WO 2005014533 A2 20050217. j) Bonnefous, C.; Payne, J. E.; Roppe, J.; Zhuang, H.; Chen, X.; Symons, K. T.; Nguyen, P. M.; Sablad, M.; Rozenkrants, N.; Zhang, Y.; Wang, L.; Severance, D.; Walsh, J. P.; Yazdani, N.; Shiau, A. K.; Noble, S. A.; Rix, P.; Rao, T. S.; Hassig, C. A.; Smith, N. D. *J. Med. Chem.* **2009**, *52*, 3047. k) Kinney, W. A.; Lee, N. E.; Blank, R. M.; Demerson, C. A.; Sarnella, C. S.; Scherer, N. T.; Nabi Mir, G.; Borella, L. E.; DiJoseph, J. F.; Wells, C. *J. Med. Chem.* **1990**, *33*, 327.

8) a) Chen, J.; Huang, D.; Ding, Y. *Tetrahedron Lett.* **2017**, *58*, 4240.

9) a) Ullmann, F. *Ber. Dtsch. Chem. Ges.* **1903**, *36*, 2382. b) Goldberg, I. *Ber. Dtsch. Chem. Ges.* **1906**, *39*, 1691.

10) a) Kosugi, M.; Kameyama, M.; Migita, T. *Chem. Lett.* **1983**, *12*, 927. b) Boger, D. L.; Duff, S. R.; Panek, J. S.; Yesuda, M. *J. Org. Chem.*, **1985**, *50***,** 5782. c) Paul, F.; Patt, J.; Hartwig, J. F. *J. Am. Chem. Soc.* **1994**, *116*, 5969. d) Guram, A. S.; Buchwald, S. L. *J. Am. Chem. Soc.* **1994**, *116*, 7901. e) Louie, J.; Hartwig, J. F. *Tetrahedron Lett.* **1995**, *36*, 3609. f) Guram, A. S.; Rennels, R. A.; Buchwald, S. L. *Angew. Chem. Int. Ed.* **1995**, *34*, 1340. g) Wolfe, J. P.; Buchwald, S. L. *J. Org. Chem.* **2000**, *65*, 1144. h) Fors, B. P.; Watson, D. A.; Biscoe, M. R.; Buchwald, S. L. *J. Am. Chem. Soc.* **2008**, *130*, 13552. i) Cheung, W. S.; Calvo, R. R.; Tounge, B. A.; Zhang, S. P.; Stone, D. R.; Brandt, M. R.; Hutchinson, T.; Flores, C. M.; Player, M. R. *Bioorg. Med. Chem. Lett.* **2008**, *18*, 4569. j) Ishikawa, M.; Furuuchi, T.; Yamauchi, M.; Yokoyama, F.; Kakui, N.; Sato, Y. *Bioorg. Med. Chem.* **2010**, *18*, 5441. k) Wenglowsky, S.; Ren, L.; Grina, J.; Hansen, J. D.; Laird, E. R.; Moreno, D.; Dinkel, V.; Gloor, S. L.; Hastings, G.; Rana, S.; Rasor, K.; Sturgis, H. L.; Voegtli, W. C.; Vigers, G.; Willis, B.; Mathieu, S.; Rudolph, J. *Bioorg. Med. Chem. Lett.* **2014**, *24*, 1923. l) Gangjee, A.; Namjoshi, O. A.; Raghavan, S.; Queener, S. F.; Kisliuk, R. L.; Cody, V. *J. Med. Chem.* **2013**, *56*, 4422.

11) a) Fleckenstein, C. A.; Plenio, H. *Chem. Soc. Rev.* **2010**, *39*, 694. b) Hartwig, J. F. *Synlett* **1997**, 329. c) Wolfe, J. P.; Wagaw, S.; Buchwald, S. L. *J. Am. Chem. Soc.* **1996**, *118*, 7215. d) Driver, M. S.; Hartwig, J. F. *J. Am. Chem. Soc.* **1996**, *118*, 7217. e) Hill, L. L.; Moore, L. R.; Huang, R. C.; Craciun, R.; Vincent, A. J.; Dixon, D. A.; Chou, J.; Woltermann, C. J.; Shaughnessy, K. H. *J. Org. Chem.* **2006**, *71*, 5117. f) Surry, D. S.; Buchwald, S. L. *Chem. Sci.* **2011**, *2*, 27. g) Marion, N.; Fremont, P. D.; Pujik, I. M.; Ecornot, E. C.; Amoroso, D.; Bell, A.; Nolan, S. P. *Adv. Synth. Catal.* **2007**, *349*, 2380.

12) a) Tye, J. W.; Weng, Z.; Johns, A. M.; Incarvito, C. D.; Hartwig, J. F. *J. Am. Chem. Soc.* **2008**, *130*, 9971. b) Strieter, E. R.; Blackmond, D. G.; Buchwald, S. L. *J. Am. Chem. Soc.* **2005**, *127*, 4120. c) Kaddouri, H.; Vicente, V.; Ouali, A.; Ouazzani, F.; Taillefer, M. *Angew. Chem., Int. Ed.* **2009**, *48*, 333. d) Barton, D. H. R.; Finet, J. P.; Khamsi, J. *Tetrahedron Lett*. **1986**, *27*, 3615. e) Barton, D. H. R.; Finet, J. P.; Khamsi, J. *Tetrahedron Lett*. **1987**, *28*, 887. f) Barton, D. H. R.; Bhatnagara, N. Y.; Finetaec, J. P.; Khamsi, J. *Tetrahedron Lett.* **1987**, *28*, 3111. g) Barton, D. H. R.; Donnelly, D. M. X.; Finet, J. P.; Guiry, P. J. *J. Chem. Soc. Perkin Trans.1*, **1991**, 2095.

13) a) Kwong, F. Y.; Klapars, A.; Buchwald, S. L. *Org. Lett.*, **2002**, *4*, 581. b) Ma, D.; Cai, Q.; Zhang, H. *Org. Lett.*, **2003**, *5*, 2453. c) Okano, K.; Tokuyama, H.; Fukuyama, T. *Org. Lett.*, **2003**, *5*, 4987. d) Jiang, D.; Fu, H.; Jiang, Y.; Zhao, Y. *J. Org. Chem.* **2007**, *72*, 672. e) Wang, Y.; Ling, J.; Zhang, Y.; Zhang, A.; Yao, Q. *Eur. J. Org. Chem.* **2015**, 4153. f) Gao, J.; Bhunia, S.; Wang, K.; Gan, L.; Xia, S.; Ma, D. *Org. Lett.* **2017**, *19*, 2809.

14) a) Yin, J.; Buchwald, S. L. *Org. Lett.*, **2000**, *2*, 1101. b) wolfe, J. P.; Rennels, R. A.; Buchwald, S. L. *Tetrahedron Lett.* **1996**, *52*, 7525. c) Yin, J.; Buchwald, S. L. *J. Am. Chem. Soc.* **2002**, *124*, 6043. d) Artamkina, G. A.; Ermolina, M. V.; Beletskaya, I. P. *Mendeleev commun.*, **2003**, *13*, 158. e) Cuny, G.; Bois-Choussy, M.; Zhu, J. *J. Am. Chem. Soc.* **2004**, *126*, 14475. f) Ikawa, T.; Barder, T. E.; Biscoe, M. R.; Buchwald, S. L. *J. Am. Chem. Soc.* **2007**, *129*, 13001. g) Shen, Q.; Hartwig, J. F. *J. Am. Chem. Soc.* **2007**, *129*, 7734. h) Fors, B. P.; Krattiger, P.; Strieter, E.; Buchwald, S. L. *Org. Lett.*, **2008**, *10*, 3505. i) Mantel, M. L. H.; Lindhardt, A. T.; Lupp, D.; Skrydstrup, T. *Chem. Eur. J.* **2010**, *16*, 5437. j) Crawford, S. M.; Lavery, C. B.; Stradiotto, M. *Chem. Eur. J.* **2013**, *19*, 16760. k) Becica, J.; Dobereiner, G. E. *ACS Catal.* **2017**, *7*, 5862.

15) a) Mamoto, T.; Kurata, Y. *Can. J. Chem.* **1983**, *61*, 86. b) Greiner, A. *Synthesis.*, **1989**, 312. c) Alvarado, P. L.; Avendano, C.; Menendez, J. C. *J. Org. Chem.* **1996**, *61*, 5865. d) Sugahara, M.; Ukita, T. *Chem. Pharm. Bull.* **1997**, *45*, 719.

16) a) Klapars, A.; Antilla, J. C.; Huang, X.; Buchwald, S. L. *J. Am. Chem. Soc.* **2001**, *123*, 7727. b) Racine, E.; Monnier, F.; Vors, J. P.; Taillefer, M. *Org. Lett.*, **2011**, *13*, 2818. c) Mangang, W.; Hua, Y.; Xinwen, Y.; Jun, W.; Zhicai, S. *Chin. J. Chem.* **2012**, *30*, 2356. d) Jiang, L. *Molecules.*, **2014**, *19*, 13448. e) Kathiravan, S.; Ghosh, S.; Hogarth, G.; Nicholls, I. A. *Chem. Commun.*, **2015**, *51*, 4834. f) Sahoo, H.; Mukherjee, S.; Grandhi, G, S.; Selvakumar, J.; Baidya, M. *J. Org. Chem.* **2017**, *82*, 2764.

17) a) Grushin, V. V.; Alper, H. *Chem. Rev.* **1994**, *94*, 1047. b) Hughes, E. C.; Veatch, F.; Elersich, V. *Ind. Eng. Chem.* **1950**, *42*, 787. c) Cramer, R.; Coulson, D. R. *J. Org. Chem.* **1975**, *40*, 2267. c) Wolfe, J. P.; Buchwald, S. L. *J. Am. Chem. Soc.* **1997**, *119*, 6054. d) Park, N. H.; Teverovskiy, G.; Buchwald, S. L. *Org. Lett.* **2014,** *16*, 220. e) Brenner, E.; Fort, Y. *Tetrahedron Lett.*, **1998**, *39*, 5359. f) Brenner, E.; Schneider, R.; Fort, Y. *Tetrahedron.,* **1999**, *55*, 12829. g) Desmarets, C.; Schneider, R.; Fort, Y. *Tetrahedron Lett.*, **2000**, *41*, 2875. h) Desmarets, C.; Schneider, R.; Fort, Y. *Tetrahedron.*, **2002**, *58*, 6913. i) Gradel, B.; Brenner, E.; Schneider, R.; Fort, Y. *Tetrahedron Lett.*, **2001**, *42*, 5689. j) Kuhl, S.; Fort, Y.; Schneider, R. *J. Organomet. Chem.*, **2005**, *690*, 6169. k) Desmarets, C.; Schneider, R.; Fort, R. *J. Org. Chem.*, **2002**, *67*, 3029. l) Amrani, R. M.; Thomas, A.; Brenner, E.; Schneider, R.; Fort, Y. *Org. Lett.*, **2003**, *5*, 2311. m) Lipshutz, B. H.; Ueda, H. *Angew. Chem. Int. Ed.* **2000**, *39*, 4492. n) Gao, C. Y.; Cao, X.; Yang, L. M. *Org. Biomol. Chem.*, **2009**, *7*, 3922. o) Chen, C.; Yang, L. M. *Org. Lett.*, **2005**, *7*, 2209. p) Chen, C.; Yang, L. M. *J. Org. Chem.* **2007**, *72*, 6324. r) Gao, C. Y.; Yang, L. M. *J. Org. Chem*, **2008**, *73*, 1624. t) Fan, X. H.; Li, G.; Yang, L. M. *J. Organomet. Chem.*, **2011**, *696*, 2482. u) Wu, W.; Fan, X. H.; Zhang, L. P.; Yang, L. M. *RSC Adv.*, **2014**, *4*, 3364. v) Kelly, R. A.; Scott, N. M.; Gonzalez, S. D.; Stevens, E. D.; Nolan, S. P. *Organometallics*, **2005**, *24*, 3442. w) Martin, A. R.; Makida, Y.; Meiries, S.; Slawin, A. M. Z.; Nolan, S. P. *Organometallics*, **2013**, *32*, 6265. x) Martin, A. R.; Nelson, D. J.; Meiries, S.; Slawin, A. M. Z.; Nolan, S. P. *Eur. J. Org. Chem.* **2014**, 3127. y) Iglesias, M.; Prieto, A.; Nicasio, M. C. *Adv. Synth. Catal.* **2010**, *352*, 1949. z) Ge, S.; Green, R. A.; Hartwig, J. F. *J. Am. Chem. Soc.* **2014**, *136*, 1617.

18) a) Kampmann, S. S.; Sobolev, A. N.; Koutsantonis, G. A.; Stewart, S. G. *Adv. Synth. Catal.* **2014**, *356*, 1967. b) Tassone, J. P.; MacQueen, P. M.; Lavoie, C. M.; Ferguson, M. J.; McDonald, R.; Stradiotto, M. *ACS Catal.* **2017**, *7*, 6048. c) Zhang, S.; Li, X.; Sun, H. *Dalton Trans.*, **2015**, *44*, 16224. d) Ackermann, L.; Sandmann, R.; Song, W. *Org. Lett.*, **2011**, *13*, 1784. e) Nathel, N. F. F.; Kim, J.; Hie, L.; Jiang, X.; Garg, N. K. *ACS Catal.* **2014**, *4*, 3289. f) Tadaoka, H.; Yamakawa, T.

Tetrahedron Lett. **2012**, *53*, 5531. g) Hie, L.; Ramgren, S. D.; Mesganaw, T.; Garg, N. K. *Org. Lett.*, **2012**, *14*, 4182. h) Mesganaw, T.; Silberstein, A. L.; Ramgren, S. D.; Nathel, N. F. F.; Hong, X.; Liu, P.; Garg, N. K. *Chem. Sci.*, **2011**, *2*, 1766. i) Tobisu, M.; Shimasaki, T.; Chatani, N. *Chemistry Letters.*, **2009**, *38*, 710. j) Lavoie, C. M.; Macqueen, P. M.; Stradiotto, M. *Chem. Eur. J.* **2016**, *22*, 18752.

19) a) For a themed issue on C-H activation reactions, see: *Chem. Soc. Rev.* **2011**, *40*, 1845; b) O. Daugulis, J. Roane, L. D.; Tran, *Acc. Chem. Res.* **2015**, *48*, 1053; c) G. Rouquet,; N. Chatani, *Angew. Chem. Int. Ed.* **2013**, *52*, 11726; d) X. Chen,; K. M. Engle,; D.-H. Wang,; J.-Q. Yu, *Angew. Chem. Int. Ed.* **2009**, *48*, 5094; e) G. He,; S. Y. Zhang,; W. A. Nack,; Q. Li,; G. Chen, *Angew. Chem. Int. Ed.* **2013**, *52*, 11124; f) T. W. Lyons,; M. S. Sanford, *Chem. Rev.* **2010,** *110*, 1147; g) B. Li, P. H.; Dixneuf, *Chem. Soc. Rev.* **2013**, *42*, 5744; h) Miura, M.; Satoh, T.; Hirano, K. *Bull. Chem. Soc. Jpn.* **2014**, *87*, 751; i) X. Yang,; G. Shan,; L; Wang,; Y. Rao, *Tetrahedron Lett.* **2016**, *57*, 819; j) M. R. Yadav,; R. K. Rit,; M. Shankar,; A. K. Sahoo *Asian J. Org. Chem.* **2015**, *4*, 846; k**)** V. Rajkumar,; Naveen; S. A. Babu, *ChemistrySelect* **2016**, *1*, 1207.

20) a) Castro, L. C.; M.; Chatani, N. *Chem. Lett.* **2015**, *44*, 410; b) X.-h. Cai,; B. Xie, *ARKIVOC* **2015**, *(i)*, 184; c) A. Yokota,; Y. Aihara,; N. Chatani, *J. Org. Chem.* **2014**, *79*, 11922; d) Y. Aihara,; N. Chatani, *J. Am. Chem. Soc.* **2014**, *136*, 898; e) Y.-H. Liu,; Y.-J. Liu,; S.-Y. Yan,; B.-F. Shi, *Chem. Commun.* **2015**, *51*, 11650. f) Li, M.; J. Dong, X. Huang, K. Li, Q. Wu, F. Song, J. You, *Chem. Commun.* **2014**, *50*, 3944; g) W. Song,; S. Lackner,; L. Ackermann, *Angew. Chem. Int. Ed.* **2014**, *53*, 2477; h) V. P. Reddy,; R. Qiu,; T. Iwasaki,; N. Kambe, *Org. Biomol. Chem.* **2015**, *13*, 6803.

21) a) Naveen, V.; Rajkumar,; S. A. Babu,; B. Gopalakrishnan, *J. Org. Chem.* **2016**, *81*, 12197**;** b) C. Reddy,; N. Bisht,; R. Parella,; S. A. Babu, *J. Org. Chem.* **2016**, *81*, 12143; c) R. Parella,; S. A. Babu, *J. Org. Chem.* **2015**, *80*, 12379;

22) S. Kathiravan,; S. Ghosh,; G. Hogarth,; I. A. Nicholls, *Chem. Commun.* **2015**, *51*, 4834.

23) The compounds **4a, 4b, 4d**, **4e**, **4i**, **7a**, **7b**, **7c**, **6** are known compounds. a) **4a, 4b, 4d**: Nack, W.A.; He, G.; Zhang, S.-Y.; Lu, C.; Chen, G. *Org. Lett.*, **2013**, *15*, 3440. b) **4e**: He, G.; Zhao, Y.; Zhang, S.; Lu, C.; Chen, G. *J. Am. Chem. Soc*. **2012**, *134*, 3. c) **4i**; Zhang, S.-Y.; He, G.; Nack, W.A.; Zhao, Y.; Li, Q.; Chen, G. *J. Am. Chem. Soc.* **2013**, *135*, 2124. d) **7a**; Xuan, J.; Li, B.-J.; Feng, Z.-J.; Sun, G.-D.; Ma, H.-H.; Yuan, Z.-W.; Chen, J.-R.; Lu, L.-Q.; Xiao, W.-J. *Chem. Asian J.* **2013**, *8*, 1090. e) **7b**; Alanthadkaa, A.; Maheswaria, C.U. *Adv. Synth. Catal.* **2015**, *357*, 1199. f)

7c; Zhu, C.; Wei, W.; Du, P.; Wan, X. *Tetrahedron*, **2014**, *70*, 9615. g) **6**; Zhang, L.; Zhang, Y.; Denga, Y.; Shi, F. *Catal. Sci. Technol.*, **2015**, *5*, 3226.

Chapter 2: Palladium-catalyzed desulfitative Heck reaction and synthesis of α-naphthol-based triarylmethanes.

Introduction

Triarylmethanes have gained significant attention and found applications in various branches of sciences, such as material science, natural products and medicinal chemistry.[1,2] The application and chemistry of triphenylmethyl groups was first discovered by Gomberg in 1900[2a] and triphenylmethane core is present in various dyes and fluorescent molecules.[2b-c] The fluorescent property of triphenylmethane molecules was utilized to study live cell imaging[2d-f] and as metal sensors.[2g] Further, triphenylmethane compounds were used as protecting groups in nucleoside, oligonucleotide, peptide and carbohydrate chemistry.[3a-c] Triarylmethanes have found extensive applications in medicinal chemistry and triarylmethanes found to exhibit biological activities, such as anti-cancer, antitubercular[3d-h] and potassium ion channel blocker[3i-k] (Figure 1).

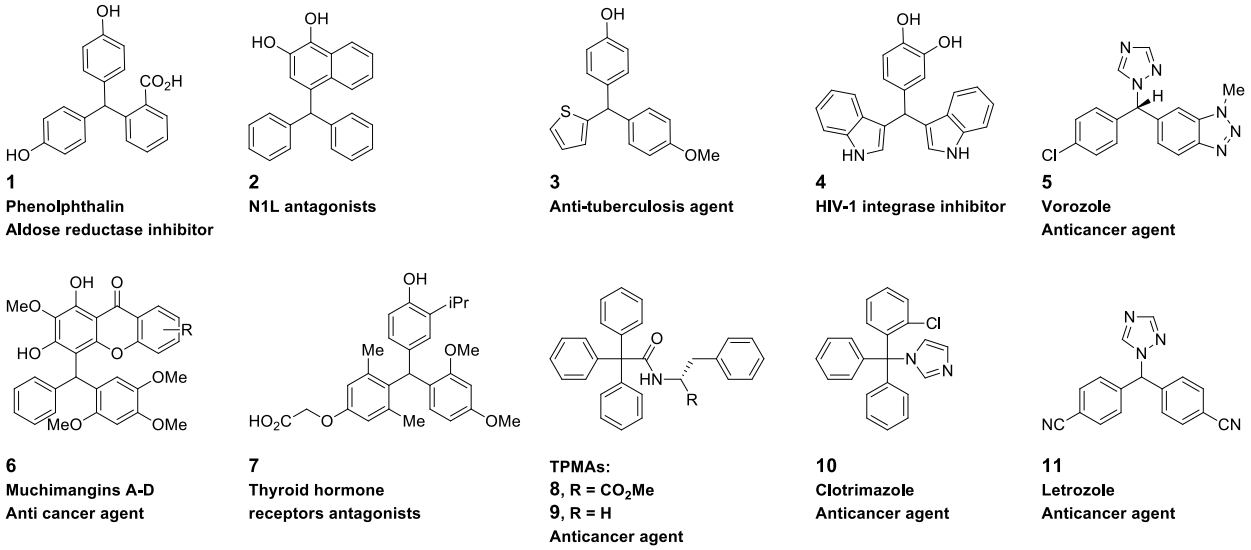
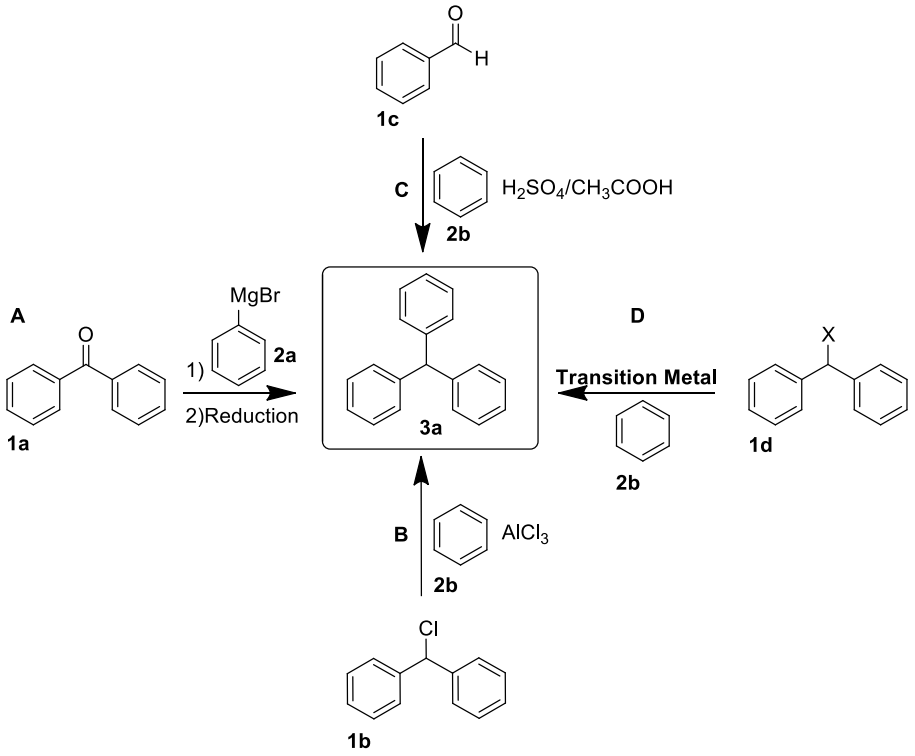


Figure 1. Representative examples of biologically active triarylmethanes.

Some of the classical synthetic routes affording triarylmethanes are given in Scheme 1. For examples, treatment of benzophenone **1a** with aryl magnesium bromide **2a** provides tritanol, further reduction of tritanol provides triphenylmethanes **3a** (Scheme 1A). Friedel-Crafts reaction is one of the most commonly employed protocol to synthesis triarylmethanes in which diarylmethyl chloride **1b** or diarylmethanol moieties reacts with benzene **2b** or electron rich aryls in presence of Lewis acids to afford triarylmethanes **3a** (Scheme 1B). Two-fold aromatic electrophilic substitution in acidic condition provides triarylmethanes **3a** (Scheme 1C). The transition metal catalyzed coupling reaction which also afforded triarylmethanes **3a** (Scheme 1D).

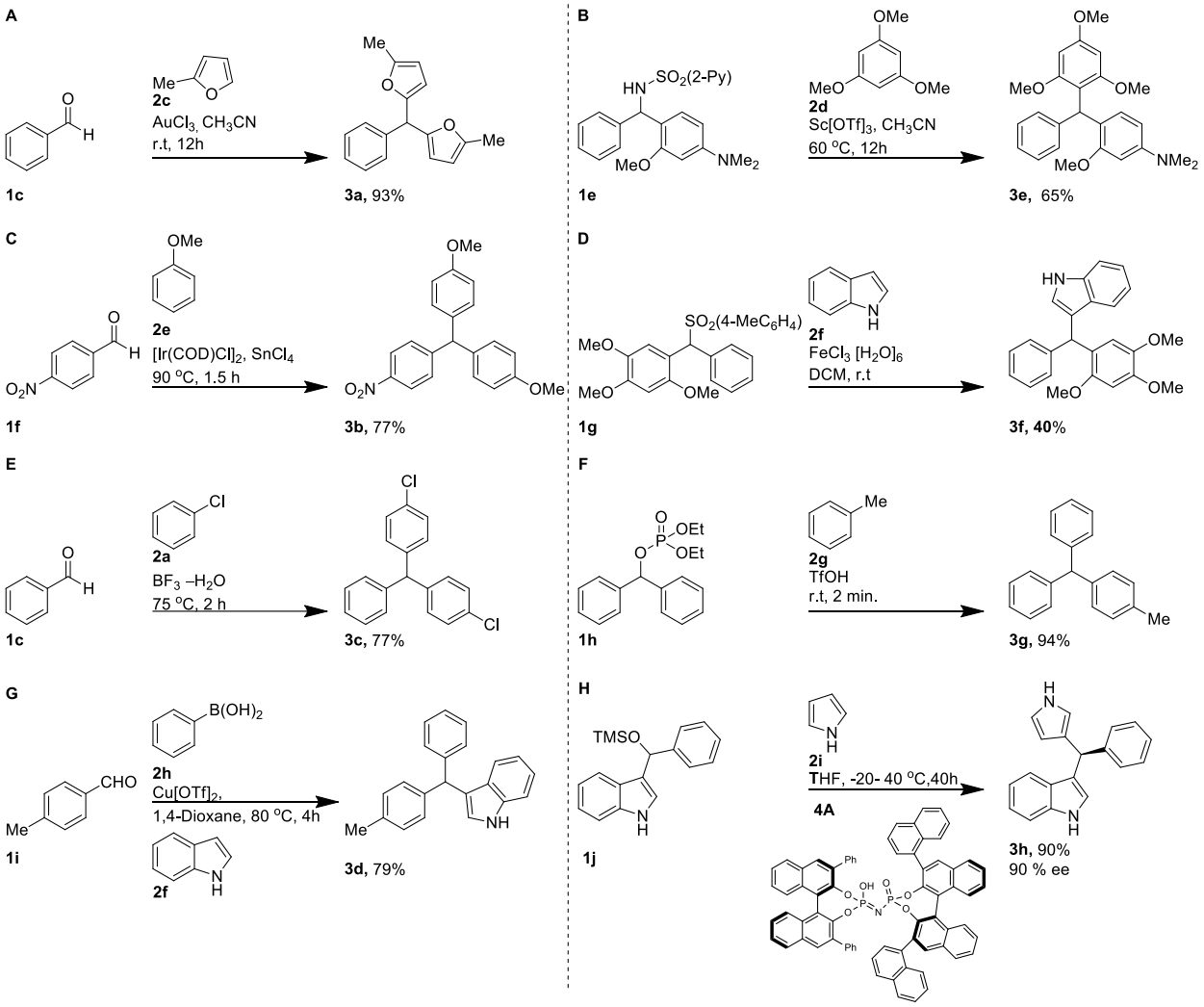
Some of the representative literature reports dealing with metal free and metal-based methods affording triarylmethanes are shown below.



Scheme 1. Synthetic routes toward triarylmethanes.

In 1926, Schaarschmidt and co-workers started utilizing concept of Friedel-Crafts reaction to synthesis triarylmethane using aryl aldehyde with benzene.[4a,b] Further the work by Hey[4c-d] and Ungnade[4e] independently reported access to substituted triarylmethane by employing functionalized aryls as well as functionalized benzaldehydes. In 1987, Roberts and Coworkers[4f] reported the Friedel-Crafts type synthesis as well as mechanistic aspects of Hey and Ungnade methods of triarylmethane synthesis.

In 2005, Nair and co-workers reported gold-promoted condensation of aryl aldehyde **1c** with electron-rich hetero aromatic compound **2c** to produce triarylmethane **3a** (Scheme 2A).[5a] In 2006, Carretero and co-workers reported the synthesis of unsymmetrical triarylmethane **3e** from diarylamine **1e** and 2,4,6-trimethoxy benzene **2d**, using copper triflate (Scheme 2B).[5b,m] Roy and co-workers reported bimetallic combination of iridium and tin {$[Ir(COD)Cl]_2/SnCl_4$} as the catalyst to access various symmetric triarylmethanes (Scheme 2C)[5c] from aryl aldehyde **1f** and anisole **2e**. In 2010, Kim and Thirupathi reported, $FeCl_3 \cdot 6H_2O$-catalyzed diaryl sulfone **1g**

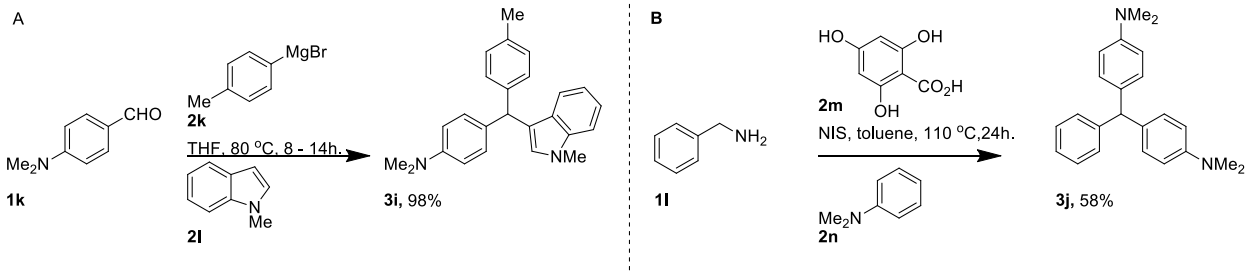


Scheme 2. Selected methods dealing on the synthesis of triarylmethanes by Friedel-Crafts and related reactions.

synthesis and the same reaction condition also enables to use diaryl sulfone as electrophile which further reacts with aryl compound to give triarylmethane **3c** (Scheme 2D).[5d] Prakash and co-workers reported BF_3-H_2O Lewis acid system to access triarylmethanes (Scheme 2E).[5e] Recently, Chakravarty and Pallikonda reported triflic acid-catalyzed Friedel-Crafts reaction of secondary benzylic phosphate **1h** with toluene **2g** to afford triarylmethane **3g (**Scheme 2F).[5f,k] Very recently, Maiti and co-workers reported multifold C-C bond formation in a three component reaction afforded indolo-triarylmethanes as well as indolocarbazole (Scheme 2G).[5g] In 2014, Zhang and Jiang reported enantioselective triarylmethane synthesis by using imidodiphosphoric acid **4A** as a chiral catalyst **(**Scheme 2H).[5h,i] There are other inevitable reports available which deal with the

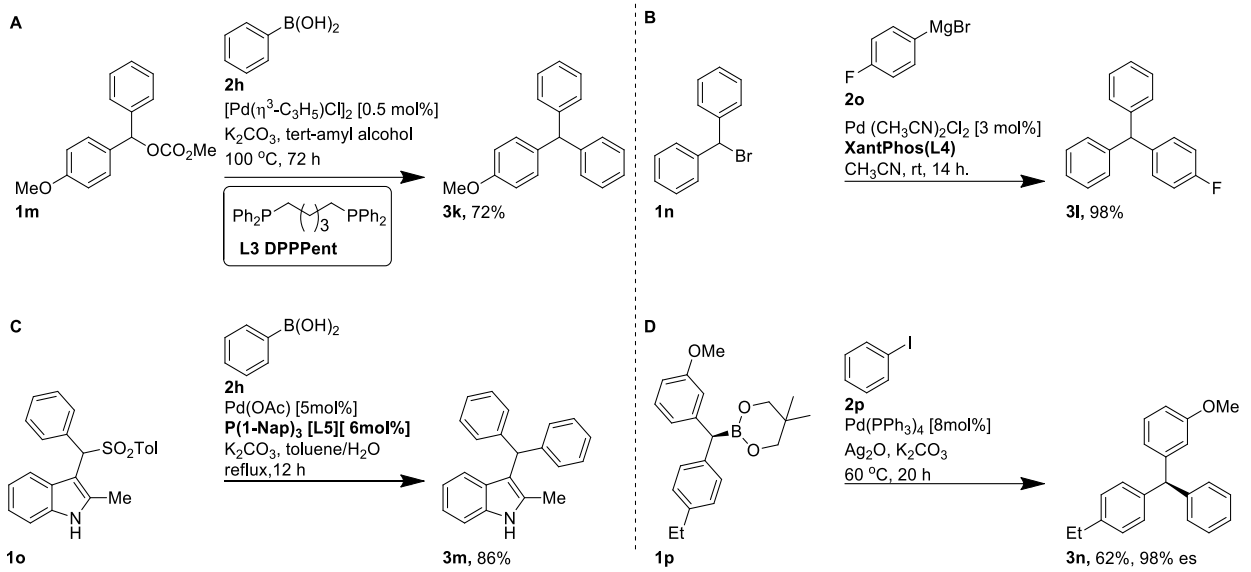
synthesis of triarylmethanes using various Lewis acid catalysts such as $FeCl_3$,[5j] $BF_3{\cdot}OEt_2$,[5l] $Sc(OTf)_3$,[5n] $SeO_2/YbCl_3$,[5o] $Bi(OTf)_3$.[5p]

In 1951, Crowley and Schick reported condensation of aryl ketones with hetero aryls in presence of strong acid such as H_2SO_4 to obtain heterotriarylmethanes[6a]. Panda and co-workers reported Grignard and Friedel-Crafts reaction-based to access aryl/heteroaryl triarylmethanes.[6b] In 1997, Katritzky and co-workers reported the synthesis of triarylmethanes via nucleophilic substitution reaction of nitrobenzene with diarylmethyl benzotriazole in presence of potassium tertiary butoxide.[6c] Recently Baire and Chinta reported the synthesis of unsymmetrical triarylmethanes via Grignard type reaction (Scheme 3A).[6d] Ogawa and co-workers reported the synthesis of unsymmetrical triarylmethanes via metal free oxidative coupling of benzylamine by using salicylic acid as co-oxidant (Scheme 3B).[6e]



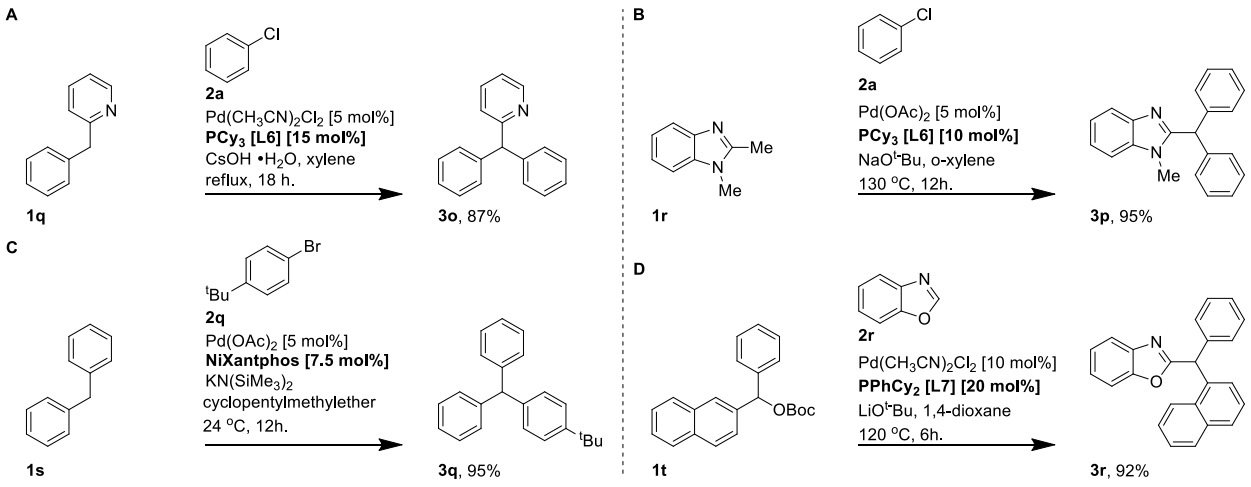
Scheme 3. Synthesis of triarylmethanes.

Suzuki Miyaura cross coupling reactions is one the powerful and fundamental method to construct C-C bonds.[7a-d.] In 2006, the first attempt to utilize this type of coupling process to synthesis triarylmethane was reported by Molander,[7e] which deals on the reaction between benzyl bromide or benzyl carbonate and potassium aryl trifluoroborates to produce diarylmethanes. But the attempt on the synthesis of triarylmethane was not fruitful and it ended with mixture of triarylmethane with bi-aryls. In 2008, Kuwano and Yu[7f] reported the synthesis of triarylmethane by using diarylmethyl carbonate **1m** as electrophile with aryl boronic acid **2h** (Scheme 4A). In 2009, Carretero and co-workers reported a palladium-catalyzed Kumada-Corriu cross coupling reaction of racemic as well as enantioenriched secondary benzylic bromides with vinyl and aryl Grignard reagent (Scheme 4B).[7g] In 2012, Jiang and Co-workers reported the synthesis of indole-based unsymmetrical triarylmethanes from the reaction of vinylogous imine, which was generated in situ from arylsulphonyl indole **1o** with aryl boronic acid **2h** (Scheme 4C).[7h] In 2014, Crudden and Co-workers reported efficient route to enantioenriched triarylmethanes via Suzuki-Miyaura coupling (Scheme 4D).[7i,j]



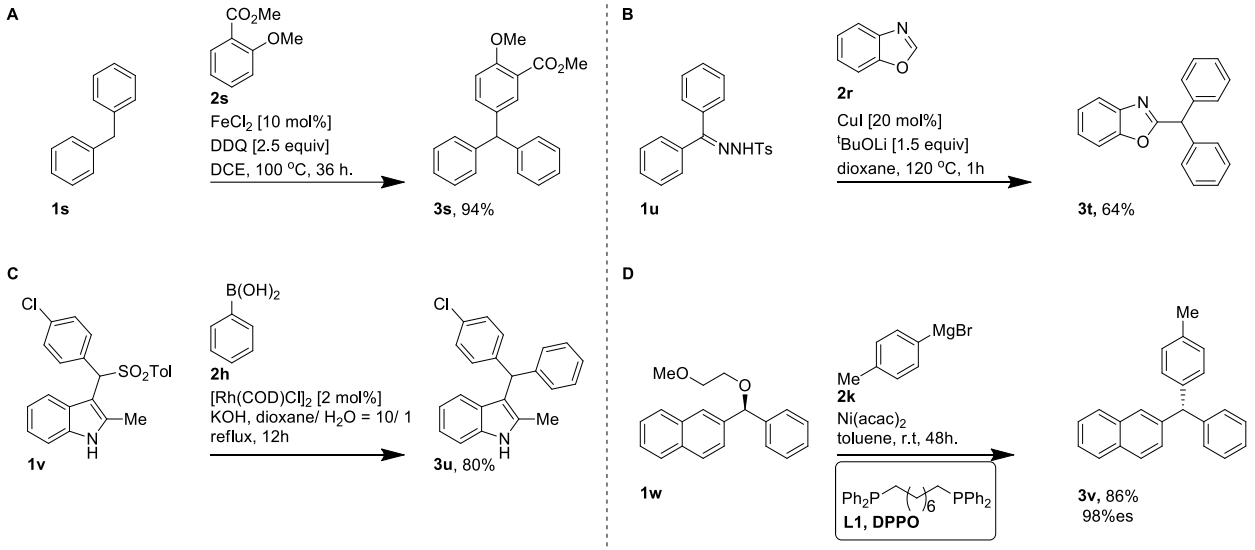
Scheme 4. Palladium-catalyzed Suzuki-Miyaura cross-coupling reactions.

C-H Functionalization is an attractive route to functionalize inert C-H bonds[8a-c] and various triarylmethanes have been synthesized by direct C-H arylation protocol (Scheme 5). In 2007, Oshima/Yorimitsu and co-workers reported the palladium-catalyzed direct C-H arylation protocol to access triarylmethanes (Scheme 5A).[8d] In 2011, Li and co-workers reported access to benzimidazole, benzoxazole and heteroaryl triarylmethanes (Scheme 5B).[8e] In 2012, Walsh and co-workers developed an efficient procedure to synthesis aryl/hetero triarylmethanes via palladium-catalyzed direct C-H functionalization (Scheme 5C).[8f-h] In 2014, Miura and co-workers reported palladium-catalyzed cross coupling of benzoxazole **2r** with electrophile diarylmethylcarbonate **1t**, which provided benzoxazole-based triarylmethane **3r** (Scheme 5D).[8i]



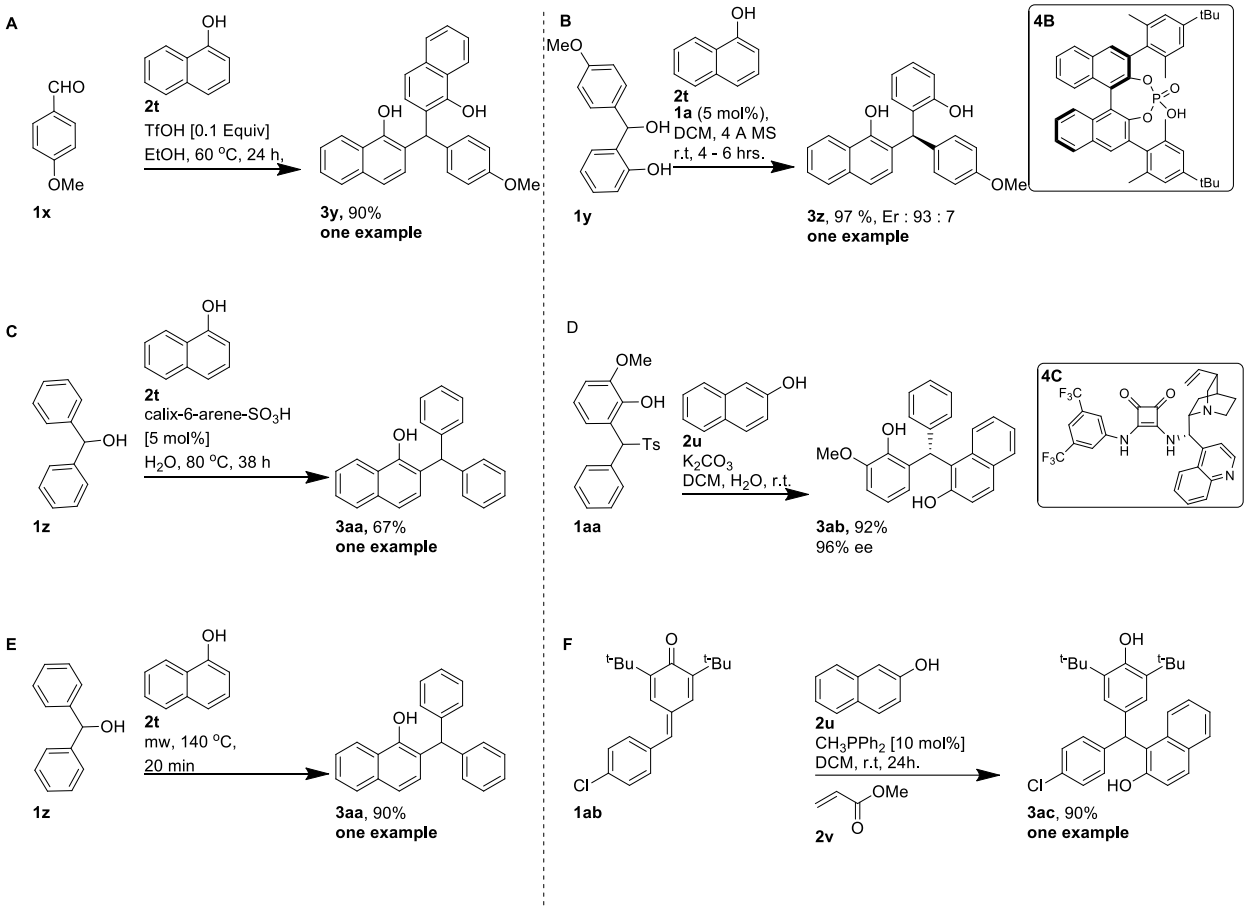
Scheme 5. Triarylmethane synthesis.

Naturally abundant transition metal such as Fe, Cu, Ni have been employed in various functional group transformations[9a-e] including the synthesis of symmetrical/unsymmetrical triarylmethanes. In 2009, Shi and co-workers developed Fe-catalyzed cross dehydrogenative coupling of diarylmethane **1s** with **2s**, which provided triarylmethanes **3s** (Scheme 6A).[9f] In 2011, Wang and co-workers developed copper-catalyzed direct C-H functionalization of benzoxazoles or its relative aryl heterocycles (Scheme 6B).[9g] Zho/Jiang reported Rh-catalyzed synthetic protocol to access indole-based triarylmethanes (Scheme 6C).[9h] In 2012, Jarvo and co-workers developed nickel-catalyzed route to access enantioenriched triarylmethane from chiral diarylmethyl ether **1w** (Scheme 6D).[9i] There are also other reports which deals with the efficient synthesis of triarylmethane using Ni[9j-k] and Cu[9l] metal catalysts.



Scheme 6. Triarylmethane synthesis.

Notably, phenol and α- or β-naphthol-based triarylmethanes also has received special applications in material science, natural products, and medicinal chemistry.[10a-h] Some of the examples of these class of compounds are given in Figure 1. In particular, some of the literature reports dealing with the synthesis of β-naphthol-based triarylmethane synthesis and α-naphthol-based triarylmethanes have been shown in Scheme 7. In 2011, Kotsuki and co-workers reported triflic acid-catalyzed condensation aldehydes with phenols and naphthols, which provided the corresponding triarylmethanes (Scheme 7A).[10i] In 2015, Schneider and co-workers reported enantioselective triarylmethane synthesis by utilizing chiral phosphoric acid catalyst **4B** (Scheme 7B).[10k] In 2008, Wang co-workers developed calix[n]arene sulphonic acid as surfactant Bronsted acid catalyst for the synthesis of α–naphthol-based triarylmethane **3aa (**Scheme 7C).[10j]

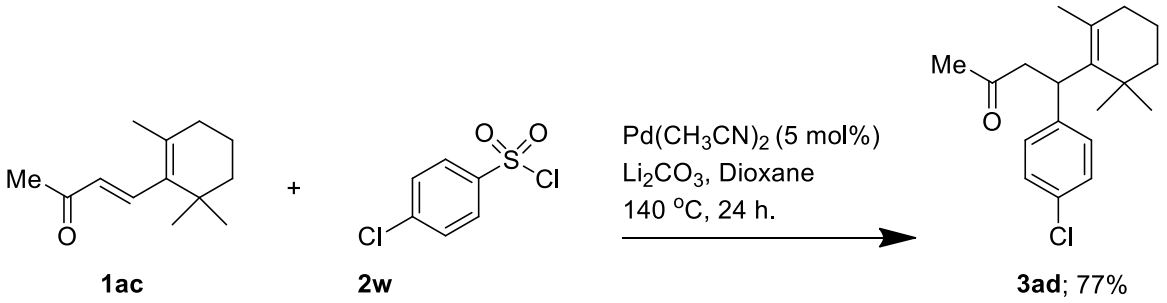


Scheme 7. Synthesis of α- or β-naphthol-based triarylmethanes.

Recently, Xu and co-workers developed efficient protocol to access various functionalized β-naphthol-based triarylmethanes (Scheme 7D).[10m] Yaragorla and co-workers reported the synthesis of an example of α–naphthol-based triarylmethane (Scheme 7E).[10l] Zhang and co-workers developed phosphine-catalyzed Friedel-Craft reaction on *p*-quinone methides **1ab** as electrophile which undergoes addition with β-naphthol **2u** to afford triarylmethane **3ac** (Scheme 7F).[10n]

Aryl sulphonyl chlorides are inexpensive compounds and have reactivity similar to aryl halides in cross-coupling reactions affording desulfitative coupling products.[11a,b] Miura and co-workers disclosed aryl sulphonyl chlorides undergo coupling reactions with suitable coupling partner under Mizoroki-Heck coupling reaction conditions.[11d-e] The aryl sulphonyl chlorides were also shown to undergo palladium-catalyzed C-C coupling reactions with suitable coupling partners under Stille,[11f] Suzuki-Miyaura,[11a] and Negishi[11g] reaction conditions. In 2009, Dong and co-workers reported Pd-catalyzed coupling of 2-arylpyridine with aryl sulphonyl chloride to provide sulfone.[11h] Cheng and co-workers reported coupling of aryl sulphonyl chloride benzoxazole, which

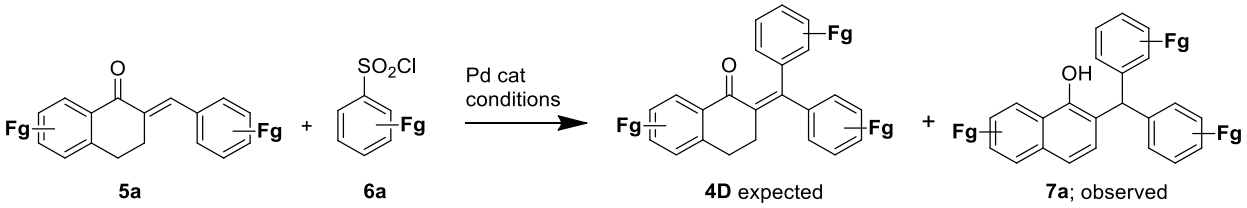
afforded arylated benzoxazole derivatives.[11i] In 2014, Doucet and Yuan reported palladium-catalyzed direct desulfitative β-arylation on thiophene and benzo[*b*]thiophene moieties.[11j] In 2015, the same group reported desulfitative coupling of enones using variety of functionalized aryl sulphonyl chlorides. For instance, reaction enone **1ac** with arylsulphonyl chloride **2w** afforded **3ad** in 77% yield (Scheme 8A).[11k]



1ac **2w** **3ad**; 77%

Scheme 8A. Desulfitative coupling reaction.

Motivated by these reports on palladium-catalyzed desulfitative coupling process it was envisaged to elaborate this concept. Accordingly, a part of this thesis reports the Pd-catalyzed desulfitative reaction of aryl sulphonyl chloride with arylidenetetralones affording an access to α-naphthol-based triarylmethanes (Scheme 8B).



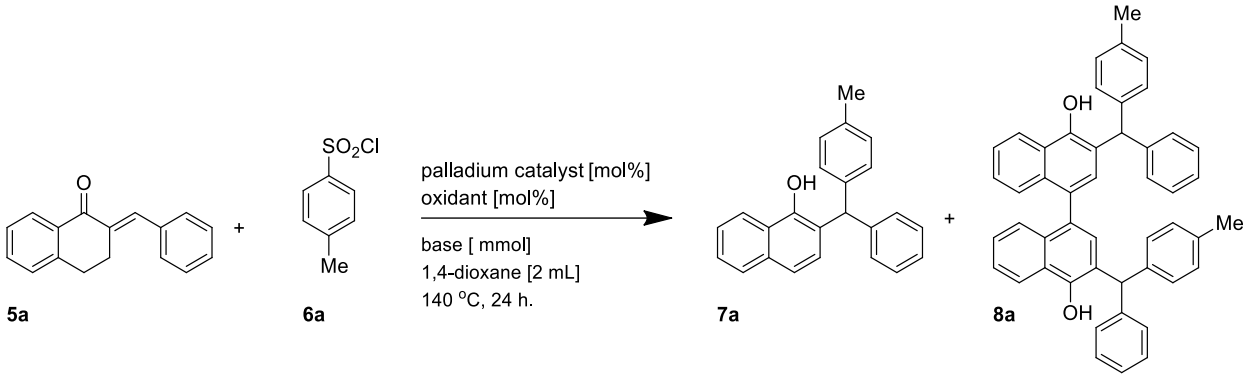
5a **6a** **4D** expected **7a**; observed

Scheme 8B. Theme of this work.

Results and Discussion

At the outset arylidenetetralone **5a** was assembled from α-tetralone and benzaldehyde using NaOH-mediated Aldol condensation. Then, arylidenetetralone **5a** was treated with *p*-toluenesulphonyl chloride **6a** in the presence of various Pd catalysts, bases, oxidants and solvents and different reaction conditions. Treatment of **5a** with **6a** and $Pd(CH_3CN)_2$ catalyst, Na_2CO_3 in 1,4-dioxane at 140 ^oC provided naphthol-based triarylmethane **7a** (Table 1, entry 1, 24% yield) instead of the expected coupling product **4D** shown in Scheme 8. Surprised by this unprecedented result, further optimization were carried out. The Pd-catalyzed reaction of **5a** with **6a** was screened using various bases, such as K_2CO_3, Li_2CO_3 and Cs_2CO_3 and the product **7a** was obtained in 33% yield when Li_2CO_3 was used as the base (entry 3). In this case, formation traces of the by-product

Table 1. Optimization of the reaction conditions. Desulfitative cross coupling of aryl sulphonyl chloride with ketone **5a**.



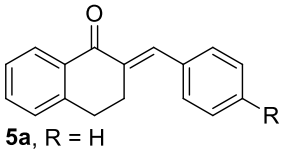
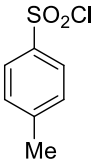
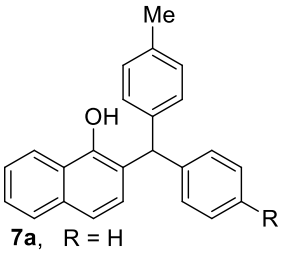
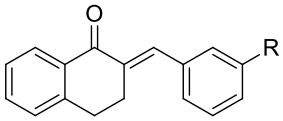
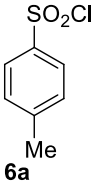
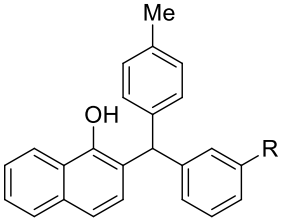
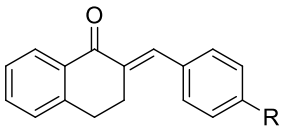
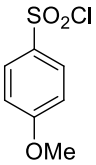
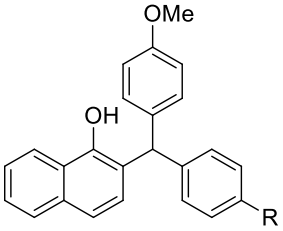
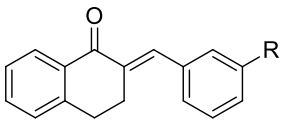
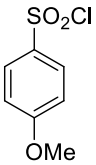
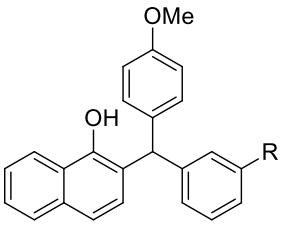
5a **6a** **7a** **8a**

Entry	Catalyst [5mol%]	*p*-TsCl [mmol]	Base [0.75 mmol]	Oxidant [10 mol%]	Yield **7a** [%]	Yield **8a** [%]
1	Pd $[CH_3CN]_2Cl_2$	0.33	Na_2CO_3	-	24	0
2	Pd $[CH_3CN]_2Cl_2$	0.33	K_2CO_3	-	12	0
3	Pd $[CH_3CN]_2Cl_2$	0.33	Li_2CO_3	-	33	8
4	Pd $[CH_3CN]_2Cl_2$	0.33	Cs_2CO_3	-	0	0
5	Pd $[CH_3CN]_2Cl_2$	0.33	Li_2CO_3	O_2	Trace	Trace
6	Pd $[CH_3CN]_2Cl_2$	0.33	Li_2CO_3	$PhI(OAc)_2$ [10]	42	8
7	Pd $[CH_3CN]_2Cl_2$	0.55	Li_2CO_3	$PhI(OAc)_2$ [10]	75	17
8	Pd $[CH_3CN]_2Cl_2$	0.55	Li_2CO_3	$PhI(OAc)_2$ [5]	37	15
9	Pd $[CH_3CN]_2Cl_2$	0.55	Li_2CO_3	MnO_2 [10]	9	Trace
10[a]	Pd $[CH_3CN]_2Cl_2$	0.55	Li_2CO_3	$PhI(OAc)_2$ [10]	11	0
11	Pd $[CH_3CN]_2Cl_2$	0.55	Li_2CO_3	$PhI(CF_3CO_2)_2$ [10]	75	15
12	Pd $[CH_3CN]_2Cl_2$	0.55	Li_2CO_3	$PhI(OAc)_2$ [20]	73	15
13	Pd $[CH_3CN]_2Cl_2$	0.55	Li_2CO_3	DDQ [20]	27	Trace
14	Pd $[CH_3CN]_2Cl_2$	0.55	Li_2CO_3	AgOAc [10]	18	35
15[b]	Pd $[CH_3CN]_2Cl_2$	0.55	Li_2CO_3	$PhI(OAc)_2$ [10]	61	19
16	Pd $[CH_3CN]_2Cl_2$	0.55	Na^tOBu	$PhI(OAc)_2$ [10]	Trace	Trace
17	Pd $[CH_3CN]_2Cl_2$	0.55	K^tOBu	$PhI(OAc)_2$ [10]	0	0
18	Pd $[CH_3CN]_2Cl_2$	0.55	NaH	$PhI(OAc)_2$ [10]	17	19
19	Pd $[OAc]_2$	0.55	Li_2CO_3	$PhI(OAc)_2$ [10]	75	15
20	$PdCl_2$	0.55	Li_2CO_3	$PhI(OAc)_2$ [10]	74	26
21	Pd $[CF_3CO_2]_2$	0.55	Li_2CO_3	$PhI(OAc)_2$ [10]	75	12
22	Pd $[PPh_3]_4$	0.55	Li_2CO_3	$PhI(OAc)_2$ [10]	77	15
23	Pd [PhCN]Cl_2	0.55	Li_2CO_3	$PhI(OAc)_2$ [10]	43	48
24	Pd $[dba]_2$	0.55	Li_2CO_3	$PhI(OAc)_2$ [10]	51	37
25[c]	Pd $[CH_3CN]_2Cl_2$	0.55	Li_2CO_3	$PhI(OAc)_2$ [10]	-	-
26[d]	Pd $[CH_3CN]_2Cl_2$	0.55	Li_2CO_3	$PhI(OAc)_2$ [10]	-	-

[a] Reaction performed at 110 °C. [b] 6 equiv of base. [c] Toluene. [d] *t*-BuOH.

8a were also observed. Next, the Pd-catalyzed reaction of **5a** with **6a** in the presence of Li_2CO_3 and other bases was screened using different oxidants (entries 5-18). The reaction condition is shown in entries 7 and 11 employing $PhI[OAc]_2$ or $PhI[CF_3CO_2]_2$ as oxidant were found to afford the product **7a** in a maximum of yield of 75% yield along with the by-product **8a** (up to 17%).

Table 2a. Scope of the desulfitative coupling of benzylidene ketones with arylsulphonyl chlorides

(*E*)-2-benzyliden-3,4 dihydronaphthalen-1(2H)-one [**5**]	aryl sulphonyl chlorides [**6**]	product [**7**]	Yield [%]	Time [h]
				
5a, R = H	**6a**	**7a**, R = H	75	24
5b, R = Br		**7b**,[a] R = Br	60	20
5c, R = Cl		**7c**,[a] R = Cl	55	22
5d, R = Me		**7d**, R = Me	30	24
5e, R = CF_3		**7e**, R = CF_3	66	16
5f, R = OCF_3		**7f**, R = OCF_3	57	18
				
5g, R = F	**6a**	**7g**, R = F	64	16
5h, R = Br		**7h**,[a] R = Br	42	16
5i, R = CF_3		**7i**, R = CF_3	60	16
				
5a, R = H	**6b**	**7j**,[a] R = H	48	20
5d, R = Me		**7k**, R = Me	40	24
5e, R = CF_3		**7l**, R = CF_3	55	15
5f, R = OCF_3		**7m**, R = OCF_3	31	16
				
5g, R = F	**6b**	**7n**, R = F	60	17
5i, R = CF_3		**7o**, R = CF_3	51	16

[a] 20 mol% of $PhI(OAc)_2$.

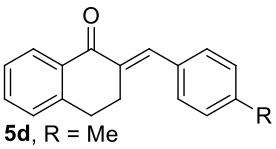
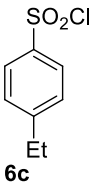
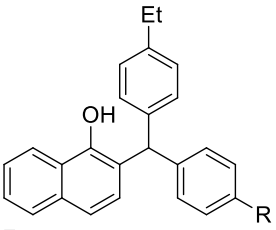
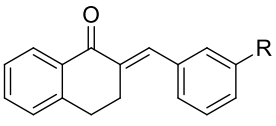
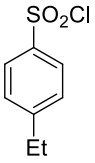
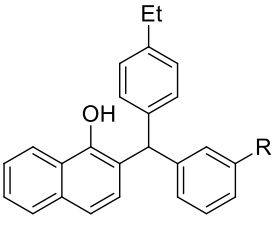
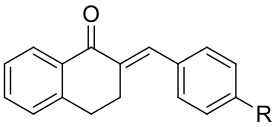
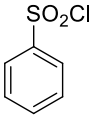
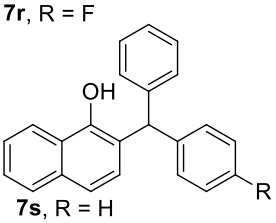
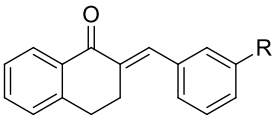
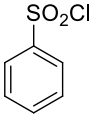
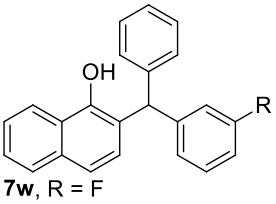
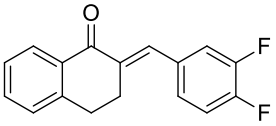
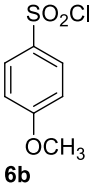
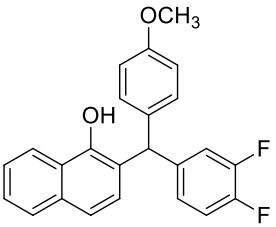
Further, the reaction of **5a** with **6a** was performed using different Pd catalysts in the presence of Li_2CO_3 as the base and these reaction afforded the product **7a** in a maximum of yield of 77% yield along with the by-product **8a** (up to 48%) (entries 19-24). The Pd-catalyzed reaction of **5a** with **6a** in toluene or *t*-BuOH was not fruitful (entries 25 and 26).

Having done the optimization reactions next, it was envisaged to investigate the scope and generality of this protocol. Accordingly, various arylidenetetralones **5a-i** were assembled and were treated with sulphonyl chlorides **6a-d** in the presence of $PdCl_2(CH_3CN)_2$ catalyst under the optimized reaction condition shown in entry 7 of Table 1. Treatment of various arylidenetetralones **5a-i** (0.25 mmol) with *p*-toluenesulfonyl chloride (2.2 equiv, 0.55 mmol) in the presence of $PdCl_2(CH_3CN)_2$ (5 mol%), $PhI(OAc)_2$ (10 mol%), and Li_2CO_3 (3 equiv, 0.75 mmol) in 1,4–dioxane (2 mL) at 140 ^{o}C afforded the corresponding naphthol-based triarylmethane derivatives **7a-i** in 30-75% yields (Table 2a). Similarly, treatment of various arylidenetetralones **5a,d-f,g,i** (0.25 mmol) with *p*-methoxybenzenesulfonyl chloride **6b** (2.2 equiv, 0.55 mmol) in the presence of $PdCl_2(CH_3CN)_2$ (5 mol%), $PhI(OAc)_2$ (10 mol%), and Li_2CO_3 (3 equiv, 0.75 mmol) in 1,4–dioxane (2 mL) at 140 ^{o}C gave the corresponding naphthol-based triarylmethane derivatives **7j-o** in 31-60% yields (Table 2a).

Further, treatment of arylidenetetralones **5d,e,g** (0.25 mmol) with *p*-ethylbenzenesulfonyl chloride **6c** (2.2 equiv, 0.55 mmol) in the presence of $PdCl_2(CH_3CN)_2$ (5 mol%), $PhI(OAc)_2$ (10 mol%), and Li_2CO_3 (3 equiv, 0.75 mmol) in 1,4–dioxane (2 mL) at 140 ^{o}C furnished the corresponding naphthol-based triarylmethane derivatives **7p-r** in 43-56% yields (Table 2b). Finally, the reaction of arylidenetetralones **5a,b,e-j** (0.25 mmol) with benzenesulfonyl chloride **6d** or **6b** (2.2 equiv, 0.55 mmol) in the presence of $PdCl_2(CH_3CN)_2$ (5 mol%), $PhI(OAc)_2$ (10 mol%), and Li_2CO_3 (3 equiv, 0.75 mmol) afforded the corresponding naphthol-based triarylmethane derivatives **7s-z** in 40-63% yields (Table 2b).

Further elaboration of substrate scope was done by performing the reactions arylidenetetralones **5l-n** (0.25 mmol) with different arylsulfonyl chlorides **6a,d** (2.2 equiv, 0.55 mmol) in the presence of $PdCl_2(CH_3CN)_2$ (5 mol%), $PhI(OAc)_2$ (10 mol%), and Li_2CO_3 (3 equiv, 0.75 mmol) in 1,4–dioxane (2 mL) at 140 ^{o}C. These reactions also furnished the corresponding naphthol-based triarylmethane derivatives **7aa-ae** in 21-62% yields (Table 3). While optimization reactions shown in Table 1 revealed that the Pd-catalyzed reaction of **5a** with **6a** gave the product **7a** along with the by-product **8a** in all the reactions (Table 2a, 2b and 3) the focus was to isolate the main product

Table 2b. Scope of the desulfitative coupling of benzylidene ketones with arylsulphonyl chlorides

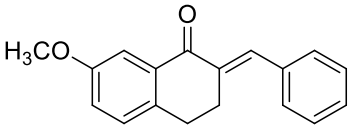
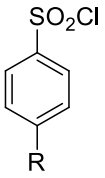
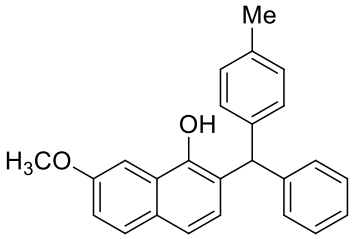
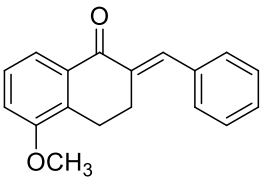
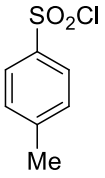
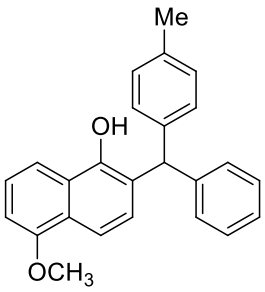
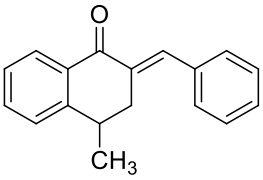
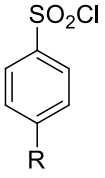
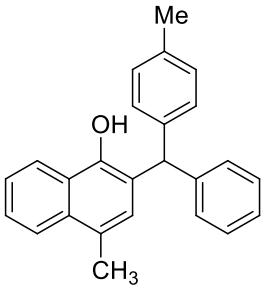
(*E*)-2-benzyliden-3,4 dihydronaphthalen-1(2H)-one [**5**]	aryl sulphonyl chlorides [**6**]	product [**7**]	Yield [%]	Time [h]
 **5d**, R = Me	 **6c**	 **7p**, R = Me	56	23
5e, R = CF_3	**6c**	**7q**, R = CF_3	50	11
 **5g**, R = F	 **6c**	 **7r**, R = F	43	16
 **5a**, R = H	 **6d**	 **7s**, R = H	55	24
5b, R = Br		**7t**,[a] R = Br	48	18
5e, R = CF_3		**7u**, R = CF_3	55	11
5f, R = OCF_3		**7v**, R = OCF_3	45	16
 **5g**, R = F	 **6d**	 **7w**, R = F	63	22
5i, R = CF_3		**7x**, R = CF_3	61	16
5h, R = Br		**7y**,[a] R = Br	40	16
 **5j**	 **6b**	 **7z**	50	16

[a] 20 mol% of $PhI(OAc)_2$.

7 in pure form. Notably, in one of the reaction, the by-product **8ab** was obtained in considerable amount than the main product **7ab**. The reason for the formation of the by-product **8ab** in the

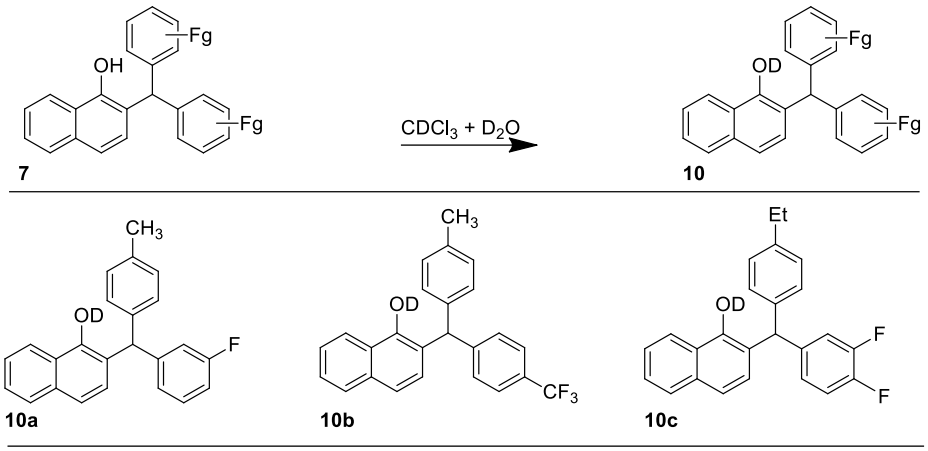
particular reaction of **5l** with **6d** was not clear at this stage. Additionally, it was noted that the naphthol-based triarylmethane derivatives **7a-z** and **7aa-7ae** are air sensitive and slowly decompose in open atmosphere in concurrence with the literature reports that α-naphthols undergo oxidation in air and also their *δ*-position are relatively reactive.[12-a-d,13a-b]

Table 3. Scope of the desulfitative coupling of benzylidene ketones with arylsulphonyl chlorides

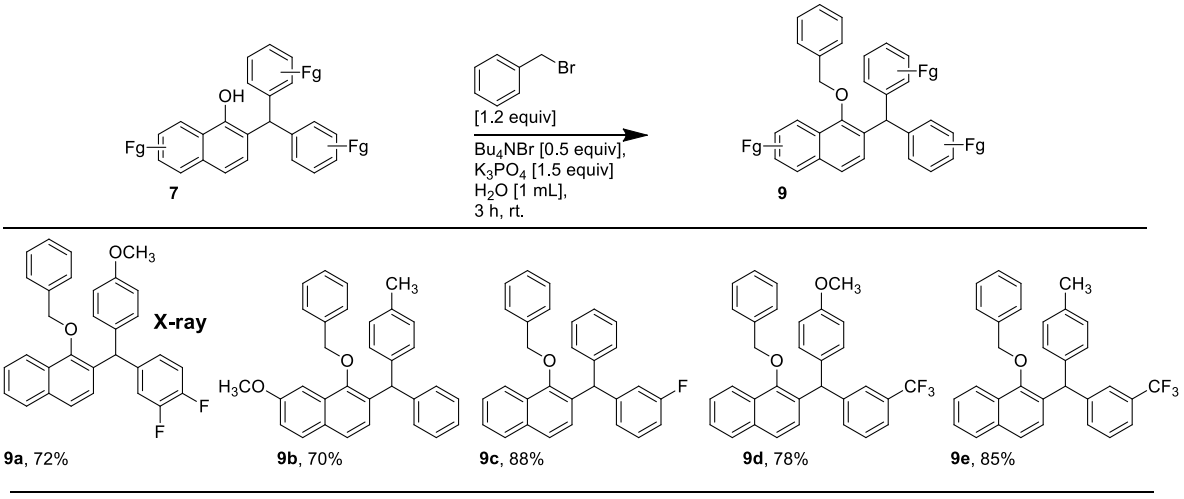
(E)-2-benzyliden-3,4 dihydronaphthalen-1(2H)-one [**5**]	Aryl sulphonyl chlorides [**6**]	Product [**7**]	Yield [%]	Time [h]
				
5l	**6a, R =Me**	**7aa**	**52**	**20**
5l	**6d, R =H**	**7ab** **8ab**	**21 [monomer]** **45 [Dimer]**	**13**
				
5m	**6a**	**7ac**	**62**	**16**
				
5n	**6a, R = Me**	**7ad**	**47**	**23**
5n	**6d, R = H**	**7ae**	**37**	**17**

Accordingly, it is assumed that the by-product e.g., **8a** and **8ab** are perhaps formed via the aerobic dimerization of their δ-position of the corresponding naphthol-based triarylmethane derivatives **7a** and **7ab**. [12a-d,13a-b]

It was necessary to confirm the structures of the naphthol-based triarylmethane derivatives obtained from the Pd-catalyzed reactions of arylidenetetralones **5** with different arylsulfonyl chlorides **6**. At first, deuterium-proton exchange was performed by recording ^{1}H NMR of representative samples of **7** in $CDCl_3$ and D_2O (Scheme 9).



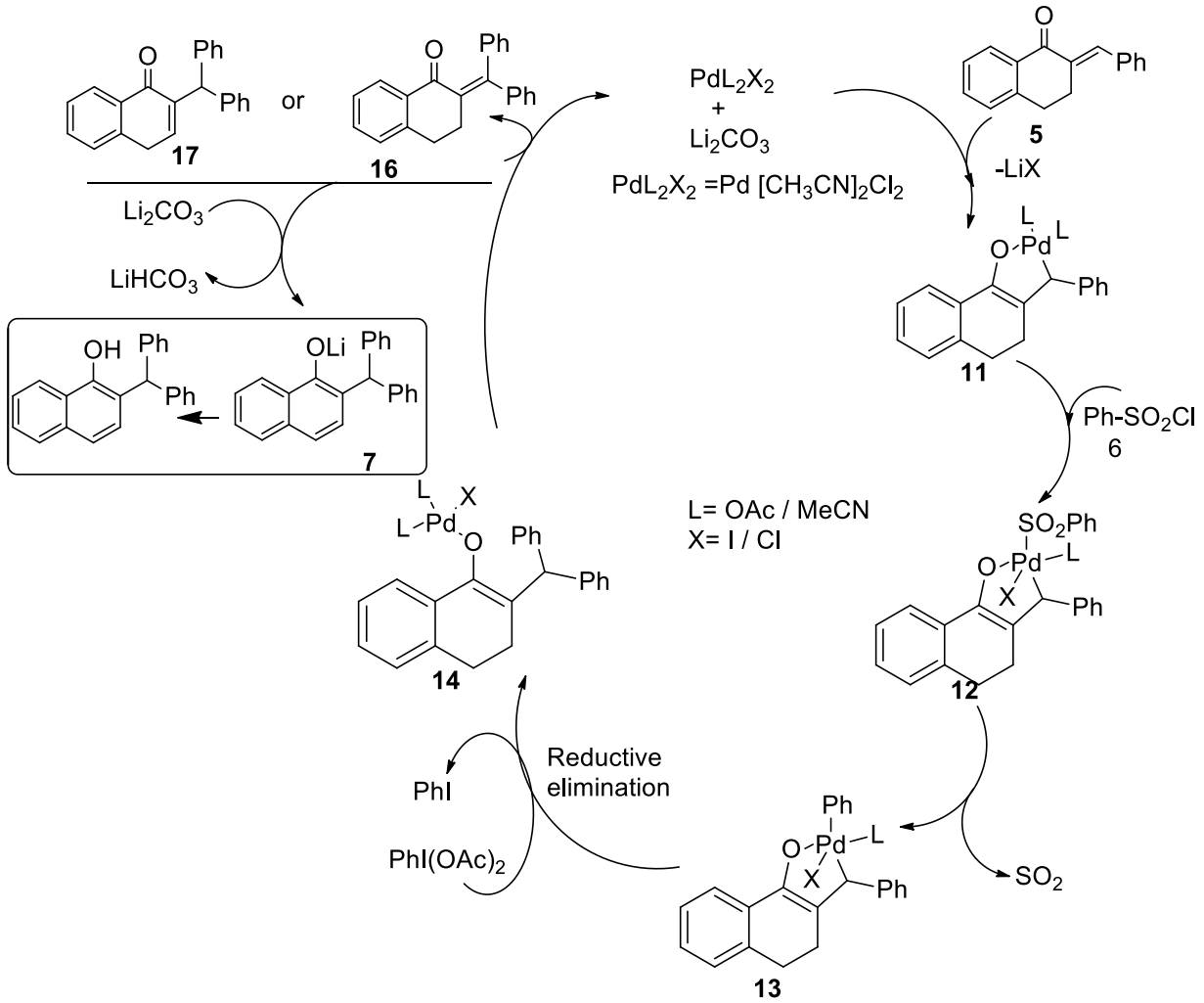
Scheme 9. Deuteration of naphthol-based triarylmethane derivatives.



Scheme 10. Synthesis of *O*-benzylated naphthol-based triarylmethane derivatives **9a-e**.

It was also necessary to show that the naphthol-based triarylmethane derivatives **7a-z** and **7aa-7ae** can be stored without any decomposition. Accordingly, some of the naphthol-based triarylmethane derivatives **7** were subjected to *O*-benzylation of OH group[14a] in the presence of benzyl bromide (Scheme 10) to afford the *O*-benzylated naphthol-based triarylmethane derivatives **9a-e** in 70-88% yields. Notably, the compound **9a** was crystallized to obtain single crystals and the structure of the compound **9a** was confirmed by single-crystal X-ray analysis.

Although an exact mechanism of this reaction comprising the Pd-catalyzed reactions of arylidenetetralones **5** with arylsulfonyl chlorides **6** is not known, a plausible mechanism is proposed in Scheme 11. The coordination of Pd[II] with **5** provides intermediate **11**. Next oxidative addition of **11** with arylsulphonyl chlorides generates the Pd species **12** and then elimination of SO_2 generates the Pd species **13** and then, the reductive elimination followed by ligand exchange provides intermediate **14**. Then, the Pd catalyst is regenerated with the formation of **16** or **17** from **14**. Then, the formation Li-enolate from **16** or **17** results the product **7** as observed in the reactions.

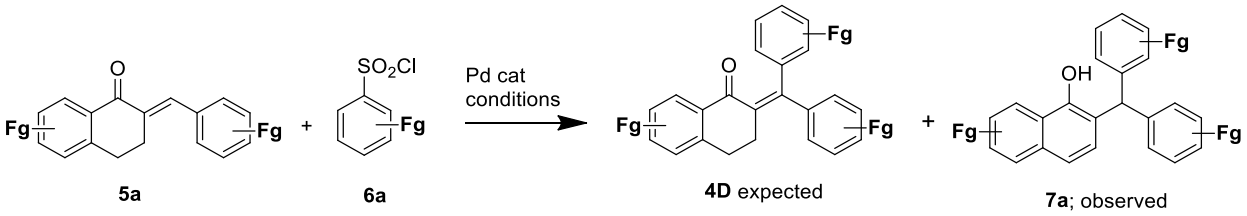


Scheme 11. Plausible reaction mechanism of desulfitative coupling reaction.

Summary

In summary, the chapter revealed the Pd-catalyzed desulfitative reaction of arylsulphonyl chloride with arylidenetetralone and this reaction afforded α-naphthol-based triarylmethane derivatives instead of Heck arylated product. The scope and generality of this protocol was investigated and

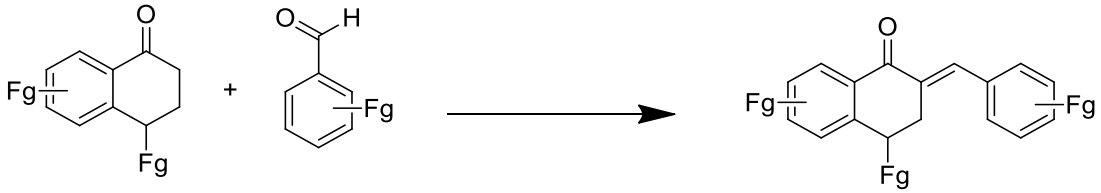
various arylidenetetralones were assembled and were treated with sulphonyl chlorides in the presence of $PdCl_2(CH_3CN)_2$ catalyst to afford a library of α-naphthol-based triarylmethane derivatives. A plausible mechanism was proposed for the Pd-catalyzed desulfitative reaction of arylsulphonyl chloride with arylidenetetralone, which afforded α-naphthol-based triarylmethane derivatives. Further, investigation with regard to mechanism of the formation of dimeric product e.g., **8a** and **8ab** via oxidation and establishment of utility of this protocol and the products are under progress in our lab.



General methods

IR spectra of all compounds were recorded as thin films or KBr pellets. ^{1}H and ^{13}C NMR spectra of all compounds were recorded (using TMS as an internal standard) in 400 MHz and 100 MHz spectrometers, respectively. The HRMS measurements were obtained from QTOF mass analyzer using electrospray ionization (ESI) method. Column chromatography was carried out on silica gel (100-200 mesh, eluent; EtOAc: hexane). Reactions were performed in anhydrous solvent in a closed system. Solutions were dried using anhydrous Na_2SO_4. Thin layer chromatography analysis was performed on silica gel/alumina plates and components were visualized by observation under iodine. Isolated yields of all the compounds were reported and yields were not optimized. The isolated products (**7a** – **7ac**) are colorless oils. The products are sensitive to atm and sometime decomposed. Hence, suitable measure be taken to store them after isolation.

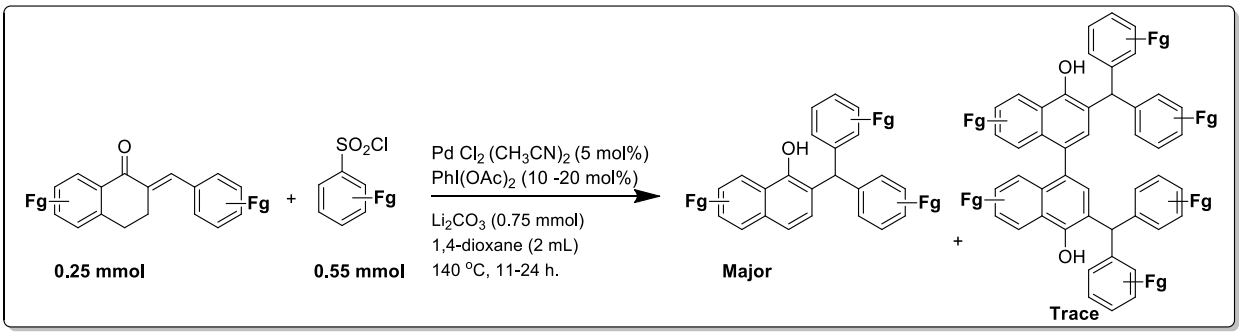
General Procedure for the synthesis of (E)-2-benzylidene-3,4-dihydronaphthalen-1(2H)-one (5)



To an oven dried round bottom flask equipped with magnetic stirrer, α-tetralone (1 equiv), aryl aldehyde (1 equiv) and EtOH. To this solution was added saturated ethanolic NaOH solution. The mixture was allowed to stir at room temperature for 30 min. Then, the precipitate was filtered and

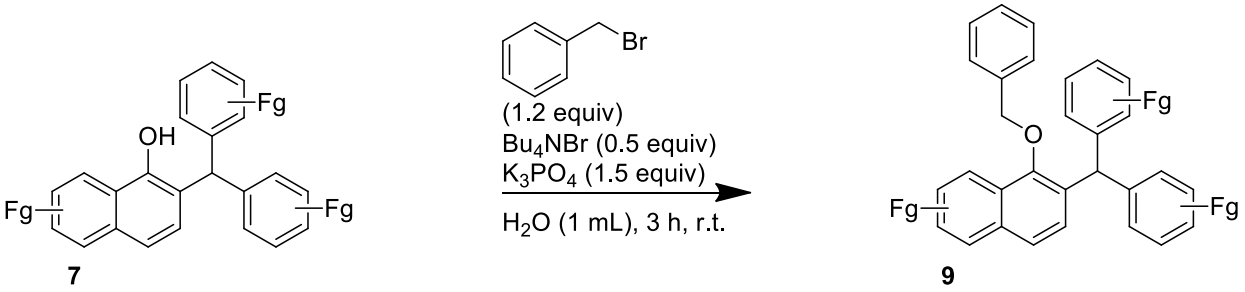
washed with cold water followed by cold methanol. The solid product was dried and used without further purification.

General Procedure for Palladium-catalyzed desulfitative reaction of arylsulfonyl chlorides with and synthesis α-naphthol-based triarylmethanes 7.



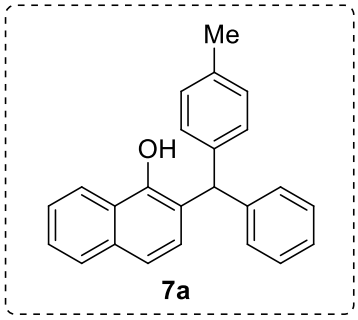
To an oven dried two neck-type round bottom flask set up (one side mounted with a condenser and the other side sealable with Teflon cap or rotaflow cap) was charged with (*E*)-2-benzylidene-3,4-dihydronaphthalen-1(2*H*)-one **5** (0.25 mmol), $PdCl_2(CH_3CN)_2$ (5 mol%), $PhI(OAc)_2$ (10 mol%), Li_2CO_3 (3 equiv, 0.75 mmol), arylsulphonyl chloride (2.2 equiv, 0.55 mmol) and dry 1,4–dioxane (2 mL) and the flask was sealed with Teflon cap. Then the reaction mixture was stirred at 140 °C for 11-24 h. After this period, the reaction mixture was allowed to attain room temperature. The reaction mixture was dissolved with 25 mL of ethyl acetate (EtOAc) and washed with brine solution (15 mL x 3), the filtrate was dried with anhydrous Na_2SO_4. Then the solution was concentrated under reduced pressure and the crude reaction mixture was immediately purified by column chromatography with silica gel (100-200 mesh, eluent; EtOAc: hexane) to afford the corresponding triarylmethanes **7**. After the isolation, the product was immediately processed to NMR analysis or to benzylation and other characterization methods. Storing the product in open atmosphere gets decomposed or oxidized, thus suggested to store at 0 °C using screw capped vials.

General Procedure Benzylation of Benzhydryl Naphthol to access air stable triarylmethanes (9a–9e)



To an oven dried round bottom flask 2-benzhydrylnaphthalene-1-ol (1 equiv), benzyl bromide (1.2 equiv), tertiarybutylammonium bromide (TBAB) (0.5 equiv), K_3PO_4 (1.5 equiv), H_2O (1 mL) were added and stirred for 3-5 h at room temperature. After this period, the reaction mixture was diluted with water and extracted with CH_2Cl_2 (15 X 3). The combined organic layer was dried with anhydrous Na_2SO_4 and concentrated under reduced pressure. The crude reaction mixture was purified by column chromatography with silica gel column (100-200 mesh, eluent; EtOAc: hexane) to afford the corresponding air stable O-benzylated α-naphthol-based triarylmethane products.

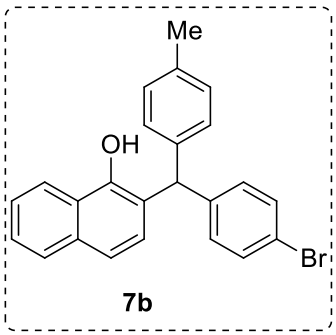
2-(4-Bromophenyl)(p-tolyl)methyl)naphthalen-1-ol (7a): Following the general procedure, **7a**



7a

was obtained after purification by column chromatography on silica gel (EtOAc:hexane = 0.3:4.7); Rf = 0.6 (EtOAc : Hex = 10:90); as a colorless oil; yield: 75% (61 mg) ; IR (KBr): 3506, 3060, 2925, 1663, 1594 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 8.18-8.15 (m, 1H), 7.83-7.80 (m, 1H), 7.52-7.48 (m, 2H), 7.42-7.29 (m,4H), 7.24 (d, 2H, *J* = 7.1 Hz), 7.19 (d, 2H, *J* = 8.0 Hz), 7.13 (d, 2H, *J* = 8.0 Hz), 7.04 (d, 1H, *J* = 8.5 Hz), 5.84 (s, 1H), 5.25 (s, 1H), 2.39 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 148.8, 142.2, 138.9, 136.8, 133.7, 129.6, 129.4, 129.3, 128.9, 128.0, 127.6, 127.0, 126.0, 125.4, 125.1, 123.6, 121.6, 120.3, 51.5, 21.1; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{24}H_{21}O$: 325.1592; found: 325.1605.

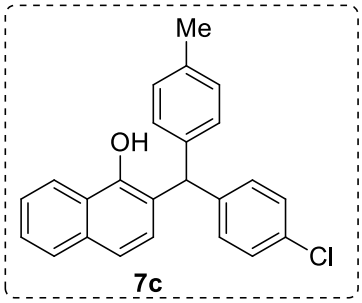
2-((4-Bromophenyl)(p-tolyl)methyl)naphthalen-1-ol (7b): Following the general procedure, **7b** was obtained after purification by column chromatography on silica gel (EtOAc:hexane = 0.3:4.7);



7b

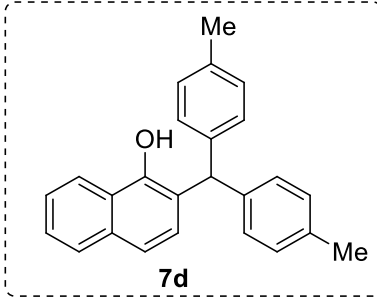
Rf = 0.6 (EtOAc : Hex = 10:90); as a colorless oil; yield: 60% (60 mg) ; IR (KBr): 3485, 3021, 2925, 1663, 1595 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 8.15 (dd, 1H, J_1 = 6.3 Hz, J_2 = 3.5 Hz), 7.83 (dd, 1H, J_1 = 6.3 Hz, J_2 = 3.5 Hz), 7.53 – 7.47 (m, 4H), 7.43 (d, 1H, *J* = 8.6 Hz), 7.19 (d, 2H, *J* = 7.9 Hz), 7.11-7.08 (m, 4H), 7.02 (d, 1H, *J* = 8.5 Hz), 5.83 (s, 1H), 5.27 (s, 1H), 2.39 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 148.7, 141.6, 138.6, 137.0, 133.7, 131.8, 131.2, 129.7, 129.2, 127.7, 127.7, 126.2, 125.6, 125.0, 123.2, 121.3, 120.8, 120.5, 50.6, 21.1; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{24}H_{20}BrO$:403.0698; found: 403.0684.

2-((4-Chlorophenyl)(p-tolyl)methyl)naphthalen-1-ol (7c): Following the general procedure, **7c** was obtained after purification by column chromatography on silica gel (EtOAc:hexane = 0.3:4.7); Rf = 0.6 (EtOAc : Hex = 10:90); as a colorless oil; yield: 55% (47 mg) ; IR (KBr): 3492, 3032, 2918, 1664, 1593 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 8.14 – 8.12 (m, 1H), 7.83 – 7.80 (m, 1H), 7.51 – 7.49 (m, 2H), 7.41 (d, 1H, *J* = 8.5 Hz), 7.34 – 7.30 (m ,2H), 7.19 – 7.08 (m, 6H), 7.00 (d, 1H, *J* = 8.5 Hz), 5.82 (s, 1H), 5.23 (s, 1H), 2.38 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 148.7, 141.0, 138.6, 137.0, 133.7, 132.7, 130.8, 129.7, 129.2, 128.9, 127.7, 126.2, 125.6, 125.0, 123.3, 121.3, 120.5, 50.6, 21.1; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{24}H_{20}ClO$: 359.1203; found 359.1155.



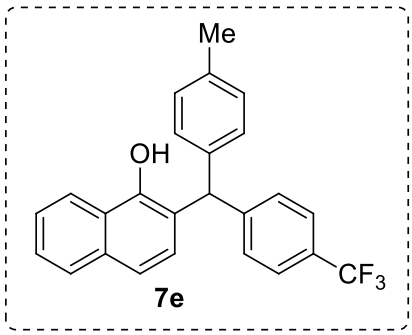
7c

2-(Di-p-tolylmethyl)naphthalen-1-ol (7d): Following the general procedure, **7d** was obtained after purification by column chromatography on silica gel (EtOAc:hexane = 0.3:4.7); Rf = 0.6 (EtOAc : Hex = 10:90); as a colorless oil; yield: 30% (20 mg) ; IR (KBr): 3495, 2961, 2864, 1663, 1592 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 8.19 (dd, 1H, J_1 = 6.2 Hz, J_2 = 3.4 Hz), 7.82 (dd, 1H, J_1 = 6.2 Hz, J_2 = 3.4 Hz), 7.51 -7.48 (m, 2H), 7.42 (d, 1H, *J* = 8.5 Hz), 7.20-7.13 (m, 8H), 7.07 (d, 1H, *J* = 8.5 Hz), 5.80 (s, 1H), 5.28 (s, 1H), 2.39 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 148.9, 139.1, 136.7, 133.7, 129.6, 129.3, 128.0, 127.6, 126.0, 125.3, 125.1, 123.7, 121.7, 120.2, 51.3, 21.1; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{25}H_{23}O$: 339.1749; found: 339.1737.



7d

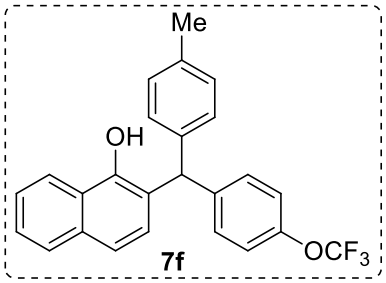
2-(p-Tolyl(4-(trifluoromethyl)phenyl)methyl)naphthalen-1-ol (7e): Following the general procedure, **7e** was obtained after purification by column chromatography on silica gel (EtOAc:hexane = 0.3:4.7); Rf = 0.6 (EtOAc : Hex = 10:90); as a colorless oil; yield: 66% (65 mg) ; IR (KBr): 3470, 3039, 2929, 1665, 1618 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 8.14 – 8.12 (m, 1H), 7.85 – 7.83 (m, 1H), 7.62 (d, 2H, *J* = 8.2 Hz), 7.54 – 7.51 (m, 2H), 7.44 (d, 1H, *J* = 8.6 Hz), 7.34 (d, 2H, *J* = 8.3 Hz), 7.20 (d, 2H, *J* = 8.0 Hz), 7.11 (d, 2H, *J* = 8.0 Hz), 7.01 (d, 1H, *J* = 8.5 Hz), 5.95 (s, 1H), 5.26 (br s, 1H), 2.39 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 148.7, 146.8, 138.4, 137.2, 133.7, 129.8, 129.2, 128.8, 127.8, 127.6, 126.2, 125.7, 125.6 (q, *J* = 3.7 Hz), 123.1,



7e

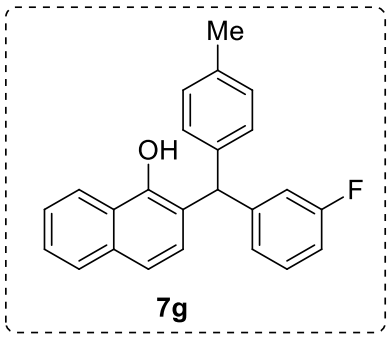
122.9, 121.2, 120.6, 50.9, 21.1; HRMS (ESI): *m/z* [M - H]$^-$ calcd for $C_{25}H_{18}F_3O$: 391.1310; found: 391.1298.

2-(p-Tolyl(4-(trifluoromethoxy)phenyl)methyl)naphthalen-1-ol (7f): Following the general procedure, **7f** was obtained after purification by column chromatography on silica gel (EtOAc:hexane = 0.3:4.7); Rf = 0.6 (EtOAc : Hex = 10:90); as a colorless oil; yield: 57% (58 mg) ; IR (KBr): cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.15 – 8.14 (m, 1H), 7.84 – 7.83 (m, 1H), 7.53 – 7.49 (m, 2H), 7.45 – 7.42 (m, 1H), 7.26 – 7.19 (m, 6H), 7.12 – 7.11 (m, 2H), 7.03 – 7.00 (m, 1H), 5.89 (s, 1H), 5.26 (s, 1H), 2.39 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 148.7, 148.0 (d, *J* = 1.8 Hz), 141.2, 138.7, 137.1, 133.7, 130.8, 129.8, 129.2, 127.7, 127.7, 126.2, 125.6, 125.0, 123.3, 121.3, 121.1, 120.5, 50.5, 21.1; HRMS (ESI): *m/z* [M - H]$^-$ calcd for $C_{25}H_{18}F_3O_2$: 407.1259; found: 407.1244.



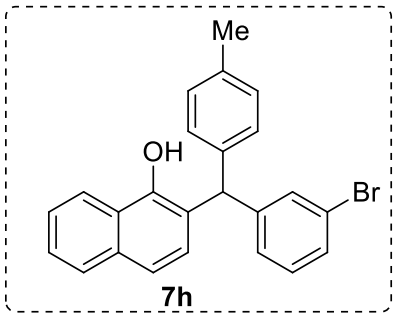
7f

2-((3-Fluorophenyl)(p-tolyl)methyl)naphthalen-1-ol (7g): Following the general procedure, 7**g** was obtained after purification by column chromatography on silica gel (EtOAc:hexane = 0.3:4.7); Rf = 0.6 (EtOAc : Hex = 10:90); as a colorless oil; yield: 64% (55 mg); IR (KBr): 3403, 2918, 2854, 1664, 1617, 1592 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.15-8.13 (m, 1H), 7.83-7.81 (m, 1H), 7.51 – 7.49 (m, 2H), 7.42 (d, 1H, *J* = 8.5 Hz), 7.34-7.28 (m, 1H), 7.18 (d, 2H, *J* = 7.7 Hz) 7.11 (d, 2H, *J* = 7.7 Hz), 7.03 – 6.97 (m, 3H), 6.92– (d, 1H, *J* = 9.6 Hz), 5.85 (s, 1H), 5.23 (s, 1H), 2.38 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 163.2 (d, *J* = 245 Hz), 148.7, 145.2 (d, *J* = 6.6 Hz), 138.5, 137.0, 133.7, 130.1 (d, *J* = 8.1 Hz), 129.7, 129.2, 127.7, 126.2, 125.6, 125.1 (d, *J* = 5 Hz), 125.1, 123.3, 121.4, 120.5, 116.4 (d, *J* = 21.5 Hz), 113.8 (d, *J* = 21.1 Hz), 51.0 (d, *J* = 1.6 Hz), 21.1; HRMS (ESI): *m/z* [M - H]$^-$ calcd for $C_{24}H_{18}FO$: 341.1342; found: 341.1329.



7g

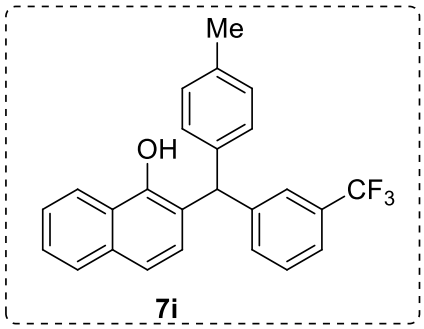
2-((3-Bromophenyl)(p-tolyl)methyl)naphthalen-1-ol (7h): Following the general procedure, **7h** was obtained after purification by column chromatography on silica gel (EtOAc:hexane = 0.3:4.7); Rf = 0.6 (EtOAc : Hex = 10:90); as a colorless oil; yield: 42% (42 mg); IR (KBr): 3440, 2925, 1662, 1510 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.14 – 8.11 (m, 1H), 7.83 – 7.81 (m, 1H), 7.52 –



7h

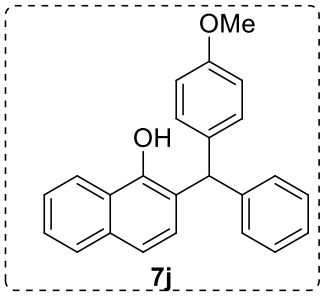
7.49 (m, 2H), 7.45 – 7.37 (m, 3H), 7.24 – 7.08 (m, 6H), 7.01 (d, 1H, *J* = 8.5 Hz), 5.83 (s, 1H), 5.21 (s, 1H), 2.38 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 148.6, 145.0, 138.3, 137.1, 133.7, 132.4, 130.2, 130.1, 129.8, 129.2, 128.1, 127.7, 127.6, 126.2, 125.6, 124.9, 123.1, 123.0, 121.3, 120.5, 50.8, 21.1; HRMS (ESI): *m/z* $[M - H]^-$ calcd for $C_{24}H_{18}BrO$: 401.0541; found: 401.0525.

2-(p-Tolyl(3-(trifluoromethyl)phenyl)methyl)naphthalen-1-ol (7i): Following the general procedure, **7i** was obtained after purification by column chromatography on silica gel (EtOAc:hexane = 0.3:4.7); Rf = 0.6 (EtOAc : Hex = 10:90); as a colorless oil; yield: 60% (59 mg); IR (KBr): 3431, 3064, 3024, 1600, 1659, 1493 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.14-8.12 (m, 1H), 7.85 – 7.83 (m, 1H), 7.58 – 7.38 (m, 7H), 7.20 (d, 2H, *J* = 8.0 Hz), 7.10 (d, 2H, *J* = 8.0 Hz), 7.00 (d, 1H, *J* = 8.5 Hz), 5.96 (s, 1H), 5.26 (s, 1H), 2.39 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 148.7, 143.7, 138.3, 137.1, 133.7, 132.8, 131 (q, J = 32 Hz), 129.8, 129.2, 129.1, 128.2, 127.8, 127.6, 126.2, 126.1 (q, J = 40 Hz), 125.7, 125.5, 125.0, 123.7 (q, *J* = 3.4 Hz), 123.2, 122.8, 121.2, 120.7, 50.8, 21.1; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{25}H_{20}F_3O$:393.1466; found: 393.1452.



7i

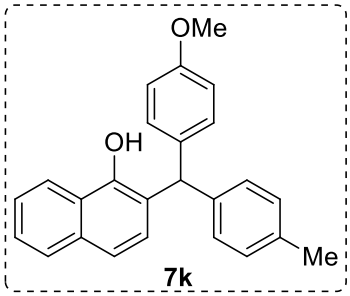
2-((4-Methoxyphenyl)(phenyl)methyl)naphthalen-1-ol (7j): Following the general procedure, **7j** was obtained after purification by column chromatography on silica gel (EtOAc:hexane = 0.3:4.7); Rf = 0.6 (EtOAc : Hex = 10:90); as a colorless oil; yield: 48% (41 mg); IR (KBr): 3452, 3064, 2929, 1663, 1595, 1510 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.17 (dd, 1H, J_1 = 6.2 Hz, J_2 = 3.4 Hz), 7.82 (dd, 1H, , J_1 = 6.2 Hz, J_2 = 3.4 Hz), 7.51 – 7.48 (m, 2H), 7.42 – 7.30 (m, 4H), 7.23 (d, 2H, *J* = 7.4 Hz), 7.15 (d, 2H, *J* =8.5 Hz), 7.03 (d, 1H, *J* = 8.5 Hz), 6.91 (d, 2H, *J* = 8.5 Hz), 5.82 (s, 1H), 5.29 (s, 1H), 3.80 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 158.6, 148.8, 142.4, 133.9, 133.7, 130.4, 129.4, 128.8, 127.9, 127.6, 125.4, 125.1, 123.7, 121.6, 120.3, 114.3, 55.3, 51.1; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{24}H_{21}O_2$:341.1542; found: 341.1529.



7j

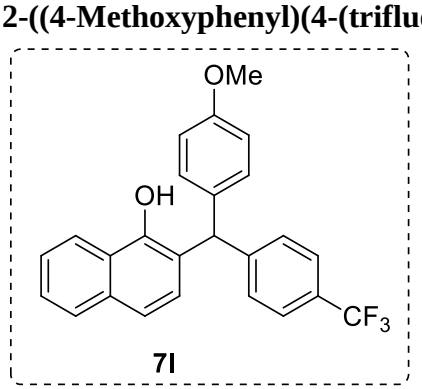
2-((4-methoxyphenyl)(p-tolyl)methyl)naphthalen-1-ol (7k): Following the general procedure, **7k** was obtained after purification by column chromatography on silica gel (EtOAc:hexane =0.3:

4.7); Rf = 0.6 (EtOAc : Hex = 10:90); as a colorless oil; yield: 40% (35 mg); IR (KBr): 3474, 3025, 2929, 2843, 1662, 1594, 1510 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 8.19 (dd, 1H, J_1 = 6.1 Hz, J_2 = 3.3 Hz), 7.82 (dd, 1H, J_1 = 6.1 Hz, J_2 = 3.3 Hz), 7.51 – 7.40 (m, 2H), 7.41 (d, 1H, J = 8.5 Hz), 7.19 – 7.11 (m, 6H), 7.04 (d, 1H, J = 8.5 Hz), 6.91 (d, 2H, J = 8.5 Hz), 5.77 (s, 1H), 5.29 (s, 1H), 3.83 (s, 3H), 2.39 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 158.6, 148.8, 139.3, 136.7, 134.1, 133.6, 130.4, 129.6, 129.2, 128.0, 127.5, 126.0, 125.4, 125.1, 123.8, 121.7, 120.2, 114.2, 55.3, 50.8, 21.1; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{25}H_{23}O_2$:355.1698; found: 355.1685 (3.6 ppm).



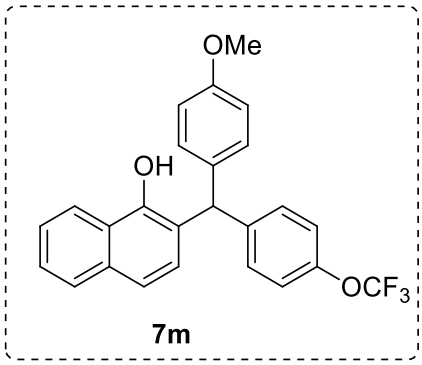
7k

2-((4-Methoxyphenyl)(4-(trifluoromethyl)phenyl)methyl)naphthalen-1-ol (7l): Following the general procedure, **7l** was obtained after purification by column chromatography on silica gel (EtOAc:hexane = 0.3:4.7); Rf = 0.6 (EtOAc : Hex = 10:90); as a colorless oil; yield: 55% (56 mg); IR (KBr): cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 8.14 – 8.11 (m, 1H), 7.84 – 7.82 (m, 1H), 7.61 (d, 2H, J = 8.2 Hz), 7.53 – 7.50 (m, 2H), 7.43 (d, 1H, J = 8.5 Hz), 7.33 (d, 2H, J = 8.2 Hz), 7.13 (d, 2H, J = 8.5 Hz), 7.00 (d, 1H, J = 8.5 Hz), 6.91 (d, 2H, J = 8.5 Hz), 5.93 (s, 1H), 5.30 (s, 1H), 3.83 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 158.8, 148.7, 147.0 (d, J = 0.9 Hz), 133.7, 133.3, 130.4, 129.8, 129.0 (q, J = 32 Hz), 127.8, 127.5, 126.2, 125.7, 125.6 (q, J = 3.9 Hz), 124.9, 123.2, 121.2, 120.6, 114.4, 55.3, 50.4; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{25}H_{20}F_3O_2$:409.1415; found: 409.1400 (3.6 ppm).



7l

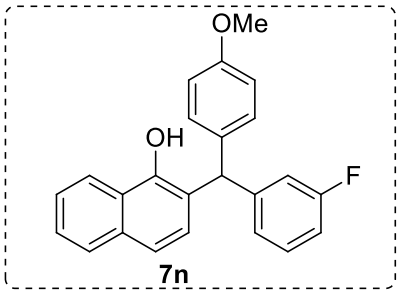
2-((4-Methoxyphenyl)(4-(trifluoromethoxy)phenyl)methyl)naphthalen-1-ol (7m): Following the general procedure, **7m** was obtained after purification by column chromatography on silica gel (EtOAc:hexane = 0.3:4.7); Rf = 0.6 (EtOAc : Hex = 10:90); as a colorless oil; yield: 31% (33 mg); IR (KBr): 3499, 2933, 1664, 1594, 1509 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 8.14 – 8.12 (m, 1H), 7.83 – 7.81 (m, 1H), 7.52 – 7.48 (m, 2H), 7.42 (d, 1H, J = 8.6 Hz), 7.23 – 7.18 (m, 4H), 7.12-7.11 (m, 2H), 6.99 (d, 1H, J = 8.5 Hz), 6.92 – 6.89 (m, 2H), 5.85 (s, 1H), 5.23 (s, 1H), 3.83 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 158.8, 148.7, 148.0 (d, J = 1.4 Hz), 141.3, 133.7, 133.5, 130.7, 130.3, 127.7, 127.6, 126.2, 125.6,



7m

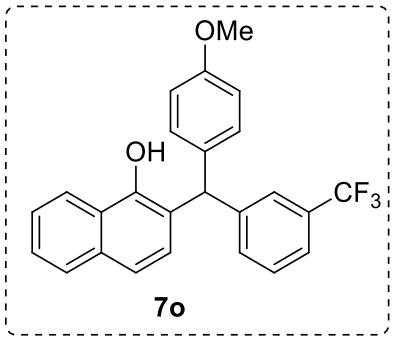
125.0, 123.3, 121.3, 121.1, 120.5, 114.4, 55.3, 50.1; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{25}H_{20}F_3O_3$:425.1365; found: 425.1349.

2-((3-Fluorophenyl)(4-methoxyphenyl)methyl)naphthalen-1-ol (7n): Following the general procedure, **7n** was obtained after purification by column chromatography on silica gel (EtOAc:hexane = 0.3:4.7); Rf = 0.6 (EtOAc : Hex = 10:90); as a colorless oil; yield: 60% (58 mg); IR (KBr): cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 8.15-8.12 (m, 1H), 7.82-7.80 (m, 1H), 7.52 – 7.48 (m, 2H), 7.41 (d, 1H, *J* = 8.6 Hz), 7.34 – 7.28 (m, 1H), 7.13 (d, 2H, *J* = 8.6 Hz), 7.01 – 6.96 (m, 3H), 6.91 – 6.89 (m, 3H), 5.83 (s, 1H), 5.23 (s, 1H), 3.83 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 163.1 (d, J = 250 Hz), 158.7, 148.7, 145.3, (d, *J* = 6.7 Hz), 133.7, 133.4, 130.3, 130.2 (d, *J* = 8.2 Hz), 127.7, 127.6, 126.2, 125.5, 125.0, 125.0 (d, *J* = 2 Hz), 123.3, 121.3, 120.5, 116.4 (d, *J* = 21.7 Hz), 114.4, 113.8 (d, *J* = 21.0 Hz), 55.3, 50.5 (d, *J* = 1.2 Hz); HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{24}H_{20}FO_2$: 359.1447; found: 359.1432.



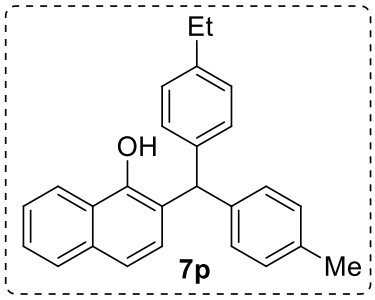
7n

2-((4-Methoxyphenyl)(3-(trifluoromethyl)phenyl)methyl)naphthalen-1-ol (7o): Following the general procedure, **7o** was obtained after purification by column chromatography on silica gel (EtOAc:hexane = 0.3:4.7); Rf = 0.6 (EtOAc : Hex = 10:90); as a colorless oil; yield: 51% (52 mg); IR (KBr): 3417, 3064, 2950, 1665, 1511 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 8.14-8.12 (m, 1H), 7.85-7.82 (m, 1H), 7.58 – 7.37 (m, 7H), 7.13 (d, 2H, *J* = 8.6 Hz), 7.00 (d, 1H, *J* = 8.6 Hz), 6.92 (d, 2H, *J* = 8.4 Hz), 5.94 (s, 1H), 5.29 (s, 1H), 3.83 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 158.8, 148.6, 143.9, 133.9, 133.3, 132.8, 131.0 (q, J = 31 Hz), 130.3, 129.1, 127.8, 127.5, 126.2, 126.1 (q, $J_=$ 3.4 Hz), 125.7, 124.9, 124.1 (q, J = 270 Hz), 123.7 (q, $J_=$ 3.4 Hz), 123.2, 121.2, 120.6, 114.5, 55.3, 50.4; HRMS (ESI): *m/z* $[M - H]^-$ calcd for $C_{25}H_{19}F_3O_2$: 407.1259; found: 407.1242.



7o

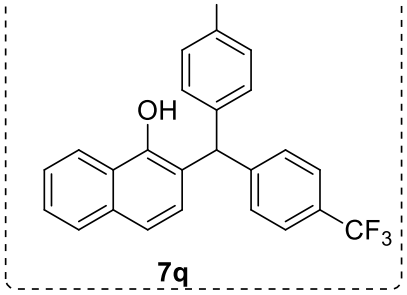
2-((4-Ethylphenyl)(p-tolyl)methyl)naphthalen-1-ol (7p): Following the general procedure, **7p** was obtained after purification by column chromatography on silica gel (EtOAc:hexane = 0.3:4.7); Rf = 0.6 (EtOAc : Hex = 10:90); as a colorless oil; yield: 56% (50 mg); IR (KBr): cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 8.18 (dd, 1H, J_1 = 6.3 Hz, J_2 = 3.5 Hz), 7.81 (dd, 1H, J_1 = 6.1 Hz, J_2 = 3.5 Hz), 7.51 – 7.48 (m, 2H), 7.41 (d, 1H, *J* = 8.5 Hz), 7.21 – 7.12 (m, 8H), 7.06 (d, 1H, *J* = 8.5 Hz), 5.79



7p

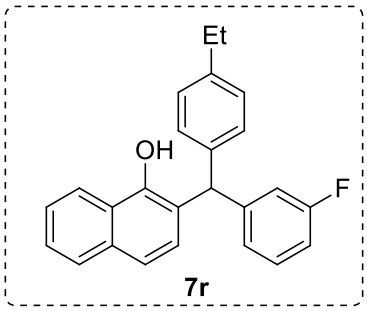
(s, 1H), 5.28 (s, 1H), 2.69 (q , 2H, J = 7.6 Hz), 2.38 (s, 3H), 1.28 (t, 3H, J = 7.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 148.9, 142.9, 139.3, 139.1, 136.7, 133.6, 129.6, 129.3, 129.26, 128.4, 128.0, 127.5, 126.0, 125.3, 125.2, 123.7, 121.7, 120.2, 51.3, 28.5, 21.1, 15.5; HRMS (ESI): *m/z* [M - H]$^-$ calcd for $C_{26}H_{23}O$: 351.1749; found: 351.1736.

2-((4-Ethylphenyl)(4-(trifluoromethyl)phenyl)methyl)naphthalen-1-ol (7q): Following the general procedure, **7q** was obtained after purification by column chromatography on silica gel (EtOAc:hexane = 0.3:4.7); Rf = 0.6 (EtOAc : Hex = 10:90); as a colorless oil; yield: 50% (50 mg); IR (KBr): 3491, 2966, 2932, 1665, 1594 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.14 – 8.12 (m, 1H), 7.85 – 7.83 (m, 1H), 7.62 (d, 2H, J = 8.2 Hz), 7.54 – 7.50 (m, 2H), 7.44 (d, 1H, J = 8.6 Hz), 7.34 (d, 2H, J = 8.1 Hz), 7.22 (d, 2H, J = 8.1 Hz), 7.13 (d, 2H, J = 8.1 Hz), 7.02 (d, 1H, J = 8.6 Hz), 5.96 (s, 1H), 5.26 (s, 1H), 2.70 (q, 2H, J = 7.6 Hz), 1.29 (t, 3H, J = 7.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 148.7, 146.8, 143.5, 138.5, 133.7, 129.8, 129.24, 129.19, 128.6, 127.8, 127.6, 126.2, 125.7, 125.6 (q, J = 4 Hz), 125.0, 123.1, 121.2, 120.6, 50.9, 28.5, 15.5; HRMS (ESI): *m/z* [M - H]$^-$ calcd for $C_{26}H_{20}F_3O$: 405.1466; found: 405.1451.



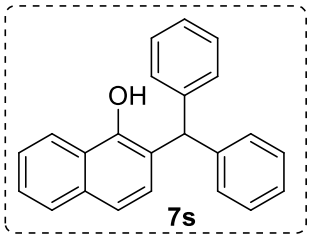
7q

2-((4-Ethylphenyl)(3-fluorophenyl)methyl)naphthalen-1-ol (7r): Following the general procedure, **7r** was obtained after purification by column chromatography on silica gel (EtOAc:hexane = 0.3:4.7); Rf = 0.6 (EtOAc : Hex = 10:90); as a colorless oil; yield: 43% (38 mg); IR (KBr): 3513, 3024, 2964, 2929, 1664, 1612, 1590 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.15 – 8.13 (m, 1H), 7.83 -7.81 (m, 1H), 7.52 – 7.49 (m, 2H), 7.42 (d, 1H, J = 8.5 Hz), 7.35 – 7.28 (m, 1H), 7.21 (d, 2H, J = 8.0 Hz), 7.13 (d, 2H, J = 8.0 Hz), 7.04 – 6.91 (m, 4H), 5.86 (s, 1H), 5.23 (s, 1H), 2.68 (q, 2H, J = 7.6 Hz), 1.28 (t, 3H, J = 7.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 163.1 (d, J = 244 Hz), 148.7, 145.2 (d, J = 6.7 Hz), 143.3, 138.6, 133.7, 130.1 (d, J = 8.3 Hz), 129.2, 128.5, 127.7 (d, J = 2.8 Hz), 126.2, 125.5, 125.1 (d, J = 2.8 Hz), 125.0, 123.2, 121.4, 120.5, 116.4 (d, J = 21.5), 113.8 (d, J = 21.1 Hz), 51.0 (d, J = 1.2 Hz), 28.5, 15.5; HRMS (ESI): *m/z* [M - H]$^-$ calcd for $C_{25}H_{20}FO$: 355.1498; found: 355.1484.

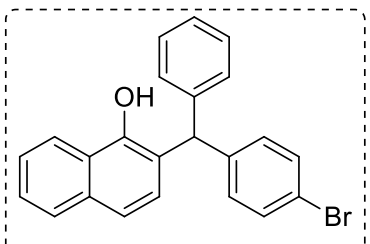


7r

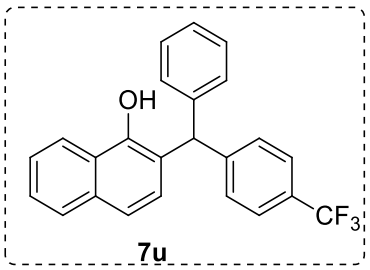
2-Benzhydrylnaphthalen-1-ol (7s): Following the general procedure, **7s** was obtained after purification by column chromatography on silica gel (EtOAc:hexane = 0.3:4.7); Rf = 0.6 (EtOAc : Hex = 10:90); as a colorless oil; yield: 55% (40 mg); IR (KBr): 3467, 3064, 1662, 1594 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 8.18 – 8.16 (m, 1H), 7.84 – 7.81 (m, 1H), 7.53 – 7.48 (m, 2H), 7.43 – 7.30 (m, 7H), 7.25 (d, 4H *J* = 6.9 Hz), 7.05 (d, 1H, *J* = 8.5 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): 148.8, 142.1, 133.7, 129.5, 128.9, 128.0, 127.6, 127.1, 126.1, 125.5, 125.1, 123.5, 121.5, 120.4, 51.7; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{23}H_{19}O$: 311.1436; found: 311.1426.



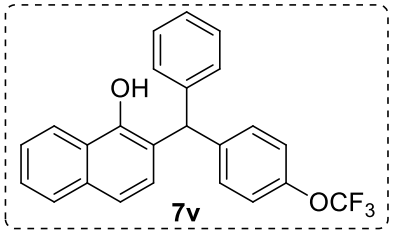
2-((4-Bromophenyl)(phenyl)methyl)naphthalen-1-ol (7t): Following the general procedure, **7t** was obtained after purification by column chromatography on silica gel (EtOAc:hexane = 0.3:4.7); Rf = 0.6 (EtOAc : Hex = 10:90); as a colorless oil; yield: 48% (46 mg); IR (KBr): 3524, 3068, 3025, 1664, 1617, 1599 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 8.13 – 8.10 (m, 1H), 7.83 – 7.81 (m, 1H), 7.51 – 7.48 (m, 4H), 7.47-7.31 (m, 4H), 7.20 (d, 2H, *J* = 7.0 Hz), 7.09 (d, 2H, *J* = 8.4 Hz), 7.00 (d, 1H, *J* = 8.4 Hz), 5.87 (s, 1H), 5.18 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 148.6, 141.7, 141.4, 133.7, 131.8, 131.2, 129.3, 129.0, 127.8, 127.7, 127.3, 126.2, 125.6, 124.9, 123.1, 121.2, 120.9, 120.6, 50.9; HRMS (ESI): *m/z* $[M - H]^-$ calcd for $C_{23}H_{16}BrO$: 387.0385; found: 387.0371.



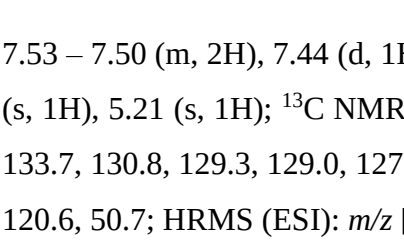
2-(Phenyl(4-(trifluoromethyl)phenyl)methyl)naphthalen-1-ol (7u): Following the general procedure, **7u** was obtained after purification by column chromatography on silica gel (EtOAc:hexane = 0.3:4.7); Rf = 0.6 (EtOAc : Hex = 10:90); as a colorless oil; yield: 55% (52 mg); IR (KBr): 3497, 3061, 2927, 1665, 1617, 1524 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 8.12 – 8.10 (m, 1H), 7.85 – 7.83 (m, 1H), 7.61 (d, 2H, *J* = 7.9 Hz), 7.53 – 7.51 (m ,2H), 7.44 (d, 1H, *J* = 8.6 Hz), 7.40 – 7.33 (m, 5H), 7.21 (d, 2H, *J* = 7.6 Hz), 7.01 (d, 1H, *J* = 8.5 Hz), 6.02 (s, 1H), 5.26 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 148.6, 146.8, 141.6, 133.7, 129.8, 129.4, 129.2, 129.0, 128.9, 127.9, 127.6, 127.3, 126.3, 125.7, 125.7, 125.6, 124.9, 123.1, 122.9, 121.0, 120.7, 51.0; HRMS (ESI): *m/z* $[M - H]^-$ calcd for $C_{24}H_{16}F_3O$: 377.1153; found: 377.1139.



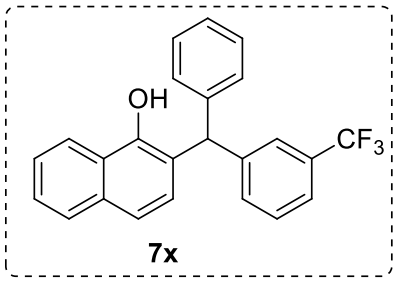
2-(Phenyl(4-(trifluoromethoxy)phenyl)methyl)naphthalen-1-ol (7v): Following the general procedure, **7v** was obtained after purification by column chromatography on silica gel (EtOAc:hexane = 0.3:4.7); Rf = 0.6 (EtOAc : Hex = 10:90); as a colorless oil; yield: 45% (44 mg); IR (KBr): 3524, 3060, 3032, 1665, 1594, 1506 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 8.14 -8.11 (m, 1H), 7.84 – 7.82 (m, 1H), 7.53 – 7.50 (m, 2H), 7.44 (d, 1H, *J* = 8.6 Hz), 7.40 – 7.19 (m, 9H), 7.01 (d, 1H, *J* = 8.6 Hz), 5.94 (s, 1H), 5.21 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 148.6, 148.1 (d, J = 1.4 Hz), 141.8, 141.0, 133.7, 130.8, 129.3, 129.0, 127.8, 127.6, 127.3, 126.2, 125.7, 124.9, 123.3, 121.1 (d, J = 3.4 Hz), 120.6, 50.7; HRMS (ESI): *m/z* $[M - H]^-$ calcd for $C_{24}H_{16}F_3O_2$: 393.1102; found: 393.1086.



2-((3-Fluorophenyl)(phenyl)methyl)naphthalen-1-ol (7w): Following the general procedure, **7w** was obtained after purification by column chromatography on silica gel (EtOAc:hexane = 0.3:4.7); Rf = 0.6 (EtOAc : Hex = 10:90); as a colorless oil; yield: 46% (52 mg); IR (KBr): cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 8.14 – 8.11 (m, 1H), 7.84 – 7.81 (m, 1H), 7.53- 7.49 (m, 2H), 7.44- 7.28 (m, 5H), 7.22 (d, 2H, *J* = 7.5 Hz), 7.03 – 6.97 (m, 3H), 6.91 (d, 1H, *J* = 10.0 Hz), 5.91 (s, 1H), 5.21 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): 163.1 (d, J = 245 Hz), 148.6, 145.0 (d, J = 7 Hz), 141.6, 133.7, 130.2 (d, *J* = 8.1 Hz), 129.3, 129.0, 127.7, 127.7, 127.3, 126.2, 125.6, 125.1 (d, *J* = 2.7 Hz), 124.9, 123.1, 121.2, 120.6, 116.5 (d, *J* = 21.8 Hz), 113.9 (d, *J* = 21.0 Hz), 51.2 (d, *J* = 1.2 Hz); HRMS (ESI): *m/z* $[M - H]^-$ calcd for $C_{23}H_{16}FO$: 327.1185; found: 327.1172 (5.8 ppm).

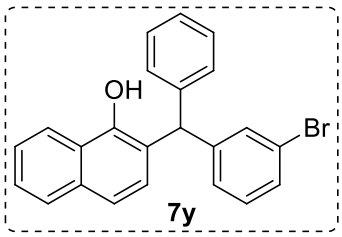


2-(Phenyl(3-(trifluoromethyl)phenyl)methyl)naphthalen-1-ol (7x): Following the general procedure, **7x** was obtained after purification by column chromatography on silica gel (EtOAc:hexane = 0.3:4.7); Rf = 0.6 (EtOAc : Hex = 10:90); as a colorless oil; yield: 61% (58 mg); IR (KBr): 3513, 3071, 3032, 1665, 1599 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 8.14 – 8.11 (m, 1H), 7.86 – 7.84 (m, 1H), 7.58 (d, 1H, J = 7.7 Hz), 7.56 – 7.32 (m, 9H), 7.22 (d, 2H, *J* = 7.1 Hz), 7.02 (d, 1H, *J* = 8.6 Hz), 6.04 (s, 1H), 5.32 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 148.6, 143.7, 141.6, 133.7, 132.9, 131.1 (q, J = 32 Hz), 129.3, 129.1, 129.0, 128.0, 127.6, 127.4, 126.3, 126.2



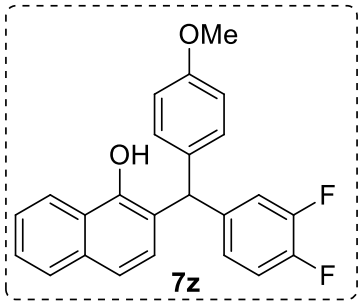
(q, J = 3.9 Hz), 125.7, 124.9, 124.1 (q, J = 271 Hz), 123.8 (q, J = 3.9 Hz), 123.2, 121.0, 120.8, 51.0 ; HRMS (ESI): *m/z* $[M - H]^-$ calcd for $C_{24}H_{16}F_3O$: 377.1153; found:377.1139.

2-((3-Bromophenyl)(phenyl)methyl)naphthalen-1-ol (7y): Following the general procedure, **7y**



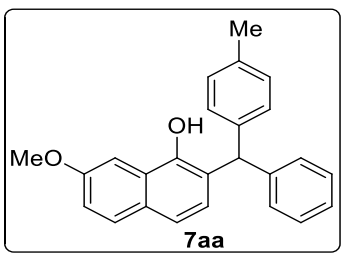
was obtained after purification by column chromatography on silica gel (EtOAc:hexane = 0.3:4.7); Rf = 0.6 (EtOAc : Hex = 10:90); as a colorless oil; yield: 40% (38 mg); IR (KBr): 3512, 3057, 1662, 1592 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 8.12 – 8.10 (m, 1H), 7.84 – 7.81 (m, 1H), 7.52 – 7.50 (m, 2H), 7.45 – 7.30 (m, 6H), 7.24 – 7.19 (m, 3H), 7.14 (d, 1H, J =7.8 Hz), 7.00 (d, 1H, J = 8.6 Hz), 5.89 (s, 1H), 5.19 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): 148.6, 144.8, 141.5, 133.7, 132.4, 130.3, 130.1, 129.3, 129.0, 128.1, 127.8, 127.7, 127.3, 126.2, 125.6, 124.9, 123.1, 123.0, 121.1, 120.6, 51.0; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{23}H_{18}BrO$: 389.0541; found: 389.0527 (3.5 ppm).

2-((3,4-Difluorophenyl)(4-methoxyphenyl)methyl)naphthalen-1-ol (7z): Following the general



procedure, **7z** was obtained after purification by column chromatography on silica gel (EtOAc:hexane = 0.3:4.7); Rf = 0.6 (EtOAc : Hex = 10:90); as a colorless oil; yield: 50% (46 mg); IR (KBr): 3435, 3078, 2950, 1664, 1513 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 8.13 – 8.10 (m, 1H), 7.83 – 7.81 (m, 1H), 7.52- 7.49 (m, 2H), 7.42 (d, 1H, J = 8.6 Hz), 7.16 – 7.10 (m, 3H), 7.02-6.89 (m, 5H), 5.82 (s, 1H), 5.26 (s, 1H) 3.83 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 158.8, 150.4 (dd, J = 251, 247 Hz), 149.2 (dd, J = 246, 246 Hz), 148.6 (d, J = 0.2 Hz), 139.8 (t, J = 4 Hz), 133.7, 133.3, 130.2, 127.8, 127.4, 126.2, 125.7, 125.2 (dd, J = 6.1 Hz), 124.9, 123.2, 121.2, 120.6, 118.3 (d, J = 17.5 Hz), 117.3 (d, J = 17.0 Hz), 114.4, 55.3, 49.8; HRMS (ESI): *m/z* $[M - H]^-$ calcd for $C_{24}H_{17}F_2O_2$: 375.1197; found: 375.1181.

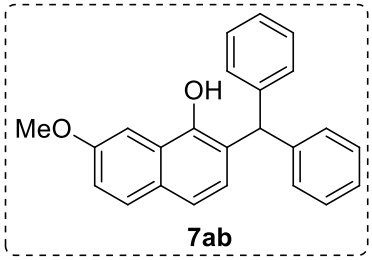
7-methoxy-2-(phenyl(p-tolyl)methyl)naphthalen-1-ol (7aa): Following the general procedure,



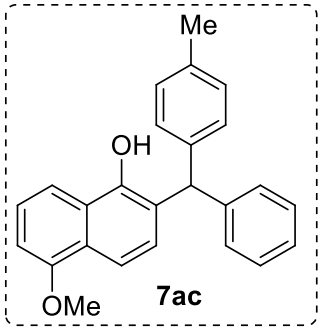
7aa was obtained after purification by column chromatography on silica gel (EtOAc:hexane = 0.3:4.7); Rf = 0.6 (EtOAc : Hex = 10:90); as a colorless oil; yield: 52% (46 mg); IR (KBr): 3399, 3025, 2921, 1657, 1594 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.71 (d, 1H, J = 8.9 Hz), 7.47 (d, 1H, J = 2.4 Hz), 7.39 – 7.31 (m, 4H), 7.24 (d, 2H, J = 7.1 Hz), 7.20 – 7.12 (m, 5H), 6.89 (d, 1H, J = 8.4 Hz), 5.79 (s, 1H), 5.15 (s, 1H),

3.93 (s, 3H), 2.38 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): 157.5, 148.0, 142.2, 138.9, 136.8, 129.7, 129.4, 129.3, 129.2, 129.1, 128.9, 127.0, 126.3, 125.6, 124.3, 120.1, 119.0, 99.9, 55.3, 51.9, 21.1; HRMS (ESI): *m/z* $[M - H]^+$ calcd for $C_{25}H_{21}O_2$: 353.1542; found:353.1527.

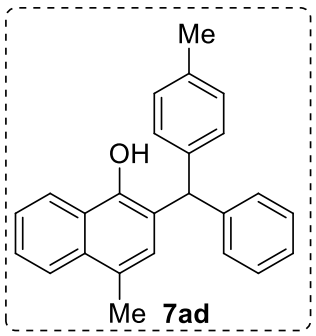
2-Benzhydryl-7-methoxynaphthalen-1-ol (7ab): Following the general procedure, **7ab** was obtained after purification by column chromatography on silica gel (EtOAc:hexane = 0.3:4.7); Rf = 0.6 (EtOAc : Hex = 10:90); as a colorless oil; yield: 22% (18 mg); IR (KBr): 3510, 3060, 2939, 1663, 1594 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.70 (d, 1H, *J* = 9.0 Hz), 7.45 (d, 1H, *J* = 2.4 Hz), 7.38 – 7.29 (m, 7H), 7.24 – 7.22 (m, 4H), 7.15 (dd, 2H, J_1 = 9.0 Hz, J_2 = 2.6 Hz), 6.87 (d, 1H, *J* = 8.5 Hz), 5.83 (s, 1H), 5.09 (s, 1H), 3.93 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): 157.6, 148.0, 142.0, 129.4, 129.2, 129.1, 128.9, 127.1, 126.1, 125.5, 124.1, 120.2, 119.0, 99.8, 55.3, 52.1; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{24}H_{21}O_2$: 341.1542; found: 341.1528.



5-Methoxy-2-(phenyl(p-tolyl)methyl)naphthalen-1-ol (7ac): Following the general procedure, **7ac** was obtained after purification by column chromatography on silica gel (EtOAc:hexane = 0.3:4.7); Rf = 0.6 (EtOAc : Hex = 10:90); as a colorless oil; yield: 62% (55 mg); IR (KBr): 3492, 2929, 1651, 1598, 1509 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.83 (d, 1H, *J* = 8.8 Hz), 7.74 (d, 1H, *J* = 8.5 Hz), 7.43 – 7.31 (m, 4H), 7.25 – 7.12 (m, 6H), 7.05 (d, 1H, *J* = 8.8 Hz), 6.85 (d, 1H, *J* = 7.6 Hz), 5.86 (s, 1H), 5.25 (s, 1H), 4.02 (s, 3H), 2.39 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 155.5, 148.6, 142.3, 139.0, 136.7, 129.6, 129.4, 129.3, 128.8, 127.3, 126.9, 126.1, 125.8, 125.5, 124.5, 114.3, 113.7, 104.0, 55.6, 51.4, 21.1; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{25}H_{23}O_2$: 355.1698; found: 355.1579.

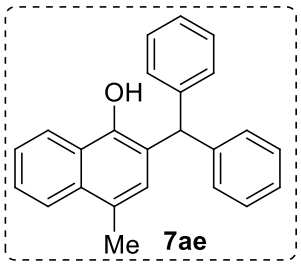


4-Methyl-2-(phenyl(p-tolyl)methyl)naphthalen-1-ol (7ad): Following the general procedure, **7ad** was obtained after purification by column chromatography on silica gel (EtOAc:hexane = 0.3:4.7); Rf = 0.6 (EtOAc : Hex = 10:90); as a colorless oil; yield: 47% (41 mg); IR (KBr): 3389, 3025, 2924, 1660, 1601, 1511 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.22 (t, 1H, *J* = 9.2 Hz), 7.96 (t, 1H, *J* = 8.9 Hz) 7.55 – 7.49 (m, 2H), 7.39 – 7.12 (m, 9H), 6.92 (d, 1H, *J* = 10.1 Hz), 5.81 (d, 1H, *J* = 10.1 Hz), 5.10 (d, 1H,

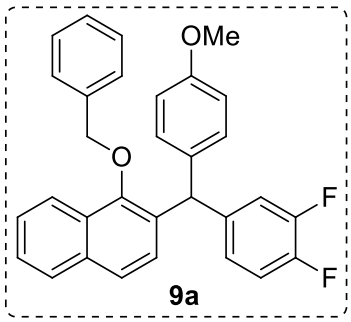


J = 4.6 Hz), 2.58 (d, 3H, *J* = 10.4 Hz), 2.40 (d, 3H, *J* = 10.4 Hz); HRMS (ESI): *m/z* [M] calcd for $C_{25}H_{22}O$: 338.1671; found: 338.1704.

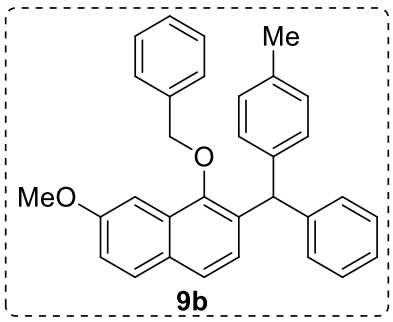
2-Benzhydryl-4-methylnaphthalen-1-ol (7ae): Following the general procedure, **7ae** was obtained after purification by column chromatography on silica gel (EtOAc:hexane = 0.3:4.7); Rf = 0.6 (EtOAc : Hex = 10:90); as a colorless oil; yield: 37% (30 mg); IR (KBr): cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 8.20 (d, 1H, *J* = 7.8 Hz), 7.95 (d, 1H, *J* = 8.1 Hz), 7.57 – 7.49 (m, 2H), 7.39 – 7.23 (m, 10H), 6.89 (s, 1H), 5.85 (s, 1H), 5.05 (s, 1H), 2.56 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 147.3, 142.2, 132.5, 129.4, 128.9, 128.4, 127.0, 126.4, 125.9, 125.5, 125.1, 124.2, 122.9, 122.1, 52.0, 19.0; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{25}H_{21}O$: 325.1592; found: 325.1580.



1-(Benzyloxy)-2-((3,4-difluorophenyl)(4-methoxyphenyl)methyl)naphthalene (9a): Following the general procedure, **9a** was obtained after purification by column chromatography on silica gel (EtOAc:hexane = 0.3:4.7); Rf = 0.6 (EtOAc : Hex = 10:90); as a colorless solid; yield: 72% (30 mg); IR (KBr): 3069, 2930, 1608, 1510 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 8.19 (d, 1H, J = 7.9 Hz), 7.88 (d, 1H, J = 7.2 Hz), 7.63 (d, 1H, *J* = 8.5 Hz), 7.58 – 7.40 (m, 7H), 7.16 – 7.04 (m, 4H), 6.93 – 6.82 (m, 4H), 6.17 (s, 1H), 4.86 (s, 2H), 3.82 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 158.3, 152.1, 150.1 (dd, *J* = 240, 240 Hz), 148.8 (dd, *J* = 240, 240 Hz), 141.5 (t, *J* = 4.7 Hz), 137.3, 135.0, 134.0, 132.0, 130.0, 128.7, 128.2, 128.2, 128.1, 127.8, 127.6, 126.3, 126.2, 125.2 (dd, *J* = 5.9 Hz), 124.3, 122.4, 118.2 (d, *J* = 17.4 Hz), 116.9 (d, *J* = 17.0 Hz), 113.9, 76.3, 55.3, 47.8; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{31}H_{25}F_2O_2$: 467.1823; found: 467.1806.

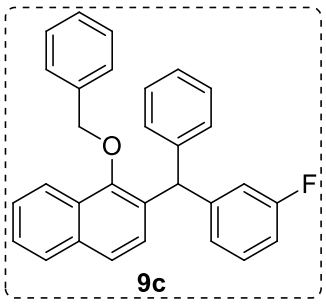


1-(Benzyloxy)-7-methoxy-2-(phenyl(p-tolyl)methyl)naphthalene (9b): Following the general procedure, **9b** was obtained after purification by column chromatography on silica gel (EtOAc:hexane = 0.3:4.7); Rf = 0.6 (EtOAc : Hex = 10:90); as a colorless oil; yield: 70% (34 mg); IR (KBr): 3065, 3026, 1627, 1510 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.76 (d, 1H, *J* = 8.9 Hz), 7.54 (d, 1H, *J* = 8.5 Hz), 7.51 – 7.40 (m, 6H), 7.33 – 7.22 (m, 3H), 7.20 – 7.07 (m, 8H), 6.29 (s, 1H), 4.85-4.78 (m, 2H), 3.85 (s, 3H), 2.36 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 158.0, 151.5,



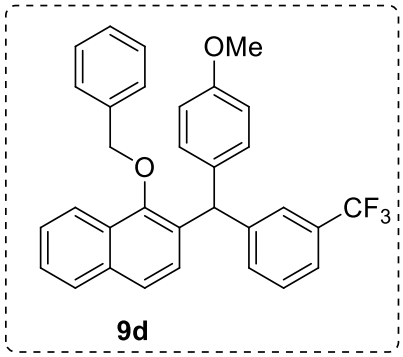
144.2, 141.0, 137.7, 135.8, 133.3, 129.7, 129.5, 129.4, 129.3, 129.2, 129.1, 128.7, 128.3, 128.2, 127.9, 126.3, 125.9, 123.8, 118.7, 100.7, 75.9, 55.2, 49.2, 21.1; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{32}H_{29}O_2$: 445.2168; found: 445.2150.

1-(Benzyloxy)-2-((3-fluorophenyl)(phenyl)methyl)naphthalene (9c): Following the general procedure, **9c** was obtained after purification by column chromatography on silica gel (EtOAc:hexane = 0.3:4.7); Rf = 0.6 (EtOAc : Hex = 10:90); as a colorless oil; yield: 88% (29 mg); IR (KBr): 3061, 3034, 1613, 1588, cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 8.20 (d, 1H, *J* = 7.6 Hz), 7.89-7.87 (m, 1H), 7.63 (d, 1H, *J* = 8.6 Hz), 7.57 – 7.38 (m, 7H), 7.34 – 7.15 (m, 8H), 6.96 – 6.92 (m, 2H), 6.87 – 6.84 (m, 1H), 6.29 (s, 1H), 4.84 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): 162.9 (d, *J* = 244 Hz), 152.2, 146.7 (d, *J* = 6.7 Hz), 143.2, 137.3, 134.0, 132.0, 129.7 (d, *J* = 8.2 Hz), 129.5, 129.1, 128.8, 128.7, 128.5, 128.2, 128.2, 128.1, 127.9, 127.8, 126.6, 126.2, 126.1, 125.2 (d, *J* = 2.7 Hz), 124.3, 122.5, 116.5 (d, *J* = 21.5 Hz), 113.3 (d, *J* = 21.0), 76.3, 49.1 (d, *J* = 1.2 Hz); HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{30}H_{24}FO$: 419.1811; found: 419.1797.



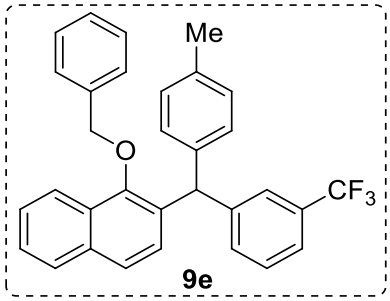
9c

1-(Benzyloxy)-2-((4-methoxyphenyl)(3-(trifluoromethyl)phenyl)methyl)naphthalene (9d): Following the general procedure, **9d** was obtained after purification by column chromatography on silica gel (EtOAc:hexane = 0.3:4.7); Rf = 0.6 (EtOAc : Hex = 10:90); as a colorless oil; yield: 78% (39 mg); IR (KBr): 3062, 2062, 1609, 1509 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 8.21 (d, 1H, *J* = 7.7 Hz), 7.89 (d, 1H, *J* = 7.3 Hz), 7.64 (d, 1H, *J* = 8.6 Hz), 7.57 – 7. 39 (m, 9H), 7.32 (d, 1H, *J* = 7.9 Hz), 7.15 (d, 1H, *J* = 8.6 Hz), 7.06 (d 2H, *J* = 8.6 Hz), 6.87 (d, 2H, *J* = 8.7 Hz), 6.27 (s, 1H), 4.86-4.82 (m, 2H), 3.82 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 158.3, 152.2, 145.4, 137.2, 135.0, 134.0, 132.8, 132.0, 130.6 (q, J = 32 Hz), 130.4, 128.7, 128.7, 128.3, 128.2, 128.1, 127.8, 127.7, 126.3, 126.2, 126.1, (q, *J* = 3.9 Hz), 124.4, 124.2 (q, J = 266 Hz), 123.2 (q, *J* = 3.9 Hz), 122.5, 113.9, 76.3, 55.3, 48.5; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{32}H_{26}F_3O_2$: 499.1885; found: 499.1898.



9d

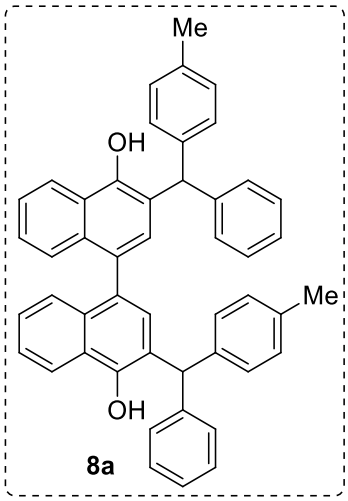
1-(Benzyloxy)-2-(p-tolyl(3-(trifluoromethyl)phenyl)methyl)naphthalene (9e): Following the general procedure, **9e** was obtained after purification by column chromatography on silica gel (EtOAc:hexane = 0.3:4.7); Rf = 0.6 (EtOAc : Hex = 10:90); as a colorless oil; yield: 85% (49



9e

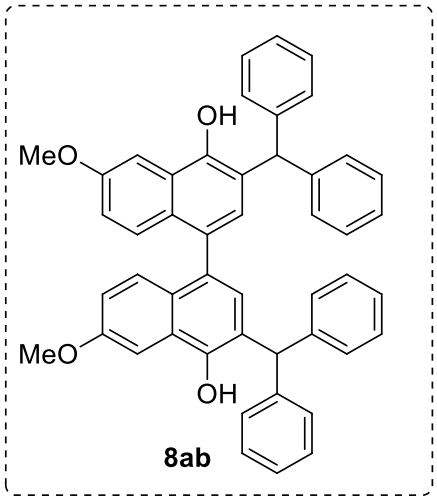
mg); IR (KBr): 3061, 2922, 1510, cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 8.21 (d, 1H, *J* = 7.8 Hz), 7.90 (d, 1H, *J* = 7.2 Hz), 7.64 (d, 1H, *J* = 8.6 Hz), 7.57 – 7.32 (m, 12H), 7.18 – 7.14 (m, 3H), 7.04 (d, 2H, *J* = 8.0 Hz), 6.29 (s, 1H), 4.91-4.82 (m, 2H), 2.37 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 152.3, 145.3, 139.9, 137.3, 136.3, 134.1, 132.8, 131.9, 130.6 (q, J = 32 Hz), 129.3 (d, *J* = 1.2 Hz), 129.1, 128.9, 128.7, 128.7, 128.5, 128.3, 128.2, 128.1, 127.8, 127.8, 126.2, 126.2, 126.1 (d, *J* = 3.9 Hz), 124.4, 124.2 (q, J = 271 Hz), 123.2 (q, *J* = 3.7 Hz), 122.5, 76.4, 48.9, 33.6, 21.1; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{32}H_{26}F_3O$: 483.1936; found: 483.1919.

3,3'-bis(phenyl(p-tolyl)methyl)-[1,1'-binaphthalene]-4,4'-diol(8a): Following the general procedure, **8a** was obtained after purification by column chromatography on silica gel (EtOAc:hexane = 0.4:4.6); Rf = 0.7 (EtOAc : Hex = 20:80); as a colorless oil; yield: 17% (14 mg); IR (KBr):3404, 3026, 1642, 1576 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 8.24 (d, 2H, *J* = 8.5 Hz), 7.48 – 7.11 (m, 24 H), 7.06-7.04 (m, 2H), 5.85 (s, 2H), 5.31 (s, 2H), 2.37 (s, 3H), 2.36 (s, 3H); HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{48}H_{39}O_2$: 647.2950; found:647.2923.



8a

3,3'-Dibenzhydryl-6,6'-dimethoxy-[1,1'-binaphthalene]-4,4'-diol (8ab): Following the general procedure, **8ab** was obtained after purification by column chromatography on silica gel (EtOAc:hexane = 0.4:4.6); Rf = 0.7 (EtOAc : Hex = 20:80); as intense red colored solid; yield: 45% (38 mg); IR (KBr): 3431, 3034, 1623, 1452 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.51 (d, 2H, *J* = 2.5 Hz), 7.37 – 7.21 (m, 22H), 6.96 (dd, 2H, J_1 = 9.2 Hz, J_2 = 2.6 Hz), 6.87 (s, 2H), 5.84 (s, 2H), 5.19 (s, 2H), 3.92 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 157.4, 147.6, 141.9, 141.9, 130.8, 129.4, 128.9, 128.9, 128.5, 128.2, 128.1 127.1, 127.1, 126.2, 123.7,



8ab

118.7, 99.9, 55.3, 52.2; HRMS (ESI): *m/z* [M + H]$^+$ calcd for $C_{48}H_{39}O_4$: 679.2848; found: 679.2873.

References

1) a) Shchepinov, M. S.; Korshun, V. A. *Chem. Soc. Rev.*, **2003**, *32*, 170. b) Kozlowski, M. C.; Morgan, B. J.; Linton, E. C. *Chem. Soc. Rev.*, **2009**, *38*, 3193. c) Mondal, S.; Panda, G. *RSC Adv.*, **2014**, *4*, 28317. d) Nambo, M.; Crudden, C. M. *ACS Catal.* **2015**, *5*, 4734. d) Duxbury, D. F.; *Chem. Rev.* **1993**, *93*, 381.

2) a) Gomberg, M. *Ber.*, **1900**, *33*, 3150. b) Muthyala, R. Katritzky, A. R. Lan, X. F. *Dyes Pigm.* **1994**, *25*, 303. c) Irie, M. *J. Am. Chem. Soc.* **1983**, *105*, 2078. d) Abe, H.; Wang, J.; Furukawa, K.; Oki, K.; Uda, M.; Tsuneda, S.; Ito, Y. *Bioconjugate Chem.* **2008**, *19*, 1219. e) Urano, Y.; Kamiya, M.; Kanda, K.; Ueno, T.; Hirose, K.; Nagano, T. *J. Am. Chem. Soc.* **2005**, *127*, 4888. f) Miura, T.; Urano, Y.; Tanaka, K.; Nagano, T.; Ohkubo, K.; Fukuzumi, S. *J. Am. Chem. Soc.* **2003**, *125*, 8666. g) Nolan, E. M.; Lippard, S. J. *Chem. Rev.* **2008**, *108*, 3443.

3) a) Stetsenko, D. A.; Lubyako, E. N.; Potapov, V. K.; Azhikina, T. L.; Sverdlov, E. D. *Tetrahedron Lett.*, *1996*, *37*, 3571. b) Shchepinov, M. S.; Case- Green, S. C.; Southern, E. M. *Nucl. Acids Res.*, **1997**, *25*, 1155. c) Greene, T. W.; Wuts, P. G. M. Protective Groups in Organic Synthesis, *3rd Edition*, *Wiley, New York*, **1999.** d) Palchaudhuri, R.; Nesterenko, V.; Hergenrother, P. J. *J. Am. Chem. Soc.* **2008**, *130*, 10274. e) Al-Qawasmeh, R. A.; Lee, Y.; Cao, M. Y.; Gu, X.; Vassilakos, A.; Wright, J. A.; Young, A. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 347. f) Shagufta. Srivastava, A. K.; Sharma, R.; Mishra, R.; Balapure, A. K.; Murthy, P. S. R.; Panda, G. *Bioorg. Med. Chem.* **2006**, *14*, 1497. g) Parai, M. K.; Panda, G.; Chaturvedi, V.; Manju, Y. K.; Sinha, S. *Bioorg. Med. Chem. Lett.* **2008**, *18*, 289. h) Dothager, R. S.; Putt, K. S.; Allen, B. J.; Leslie, B. J.; Nesterenko, V.; Hergenrother, P. J. *J. Am. Chem. Soc.* **2005**, *127*, 8686. i) Wulff, H.; Zhorov, B. *Chem. Rev.* **2008**, *108*, 1744. j) Rauer, H.; Lanigan, M. D.; Pennington, M. W.; Aiyar, J.; Ghanshani, S.; Cahalan, M. D.; Norton, R. S.; Chandy, K. G. *J. Biol. Chem.* **2000**, *275*, 1201. k) Wulff, H.; Miller, M. J.; Hänsel, W.; Grissmer, S.; Cahalan, M. D.; Chandy, G. *Proc. Natl. Acad. Sci. U. S. A.* **2000**, *97*, 8151.

4) a) Bandini, M.; Melloni, A.; Umani-Ronchi, A. *Angew. Chem. Int. Ed.* **2004**, *43*, 550. b) Schaarschmidt, A.; Herman, L.; Szemzo, B. *Ber*. **1926**, *58*, 1914. c) Hey, J. D. *J. Chem. Soc.* **1935**, 72. d) Hey, J. D.; Ellison, H. *J. Chem. Soc.* **1938**, 1847. e) Ungnade, H. F.; Crandall, E. W. *J. Am.*

Chem. Soc. **1949**, *71*, 2209. f) Roberts, R. M.; El-Khawaga, A. M.; Sweeney, K. M.; El-Zohry, M. F. *J. Org. Chem.* **1987**, *52*, 1591.

5) a) Vijay Nair.; Abhilash, K. G.; Vidya, N. *Org. Lett.*, **2005**, *7*, 5857. b) Esquivias, J.; Arrayas, R. G.; Carretero, J. C. *Angew. Chem. Int. Ed.* **2006**, *45*, 629. c) Podder, S.; Choudhury, J.; Roy, U. K.; Roy, S. *J. Org. Chem.* **2007**, *72*, 3100. d) Thirupathi, P.; Kim, S. S. *Eur. J. Org. Chem.* **2010**, 1798. e) Surya Prakash, G. K.; Panja, C.; Shakhmin, A.; Shah, E.; Mathew, T.; Olah. G. A. *J. Org. Chem.* **2009**, *74*, 8659. f) Pallikonda, G.; Chakravarty, M. *J. Org. Chem.* **2016**, *81*, 2135. g) Das, T.; Debnath, S.; Maiti, R.; Maiti, D. K. *J. Org. Chem.* **2017**, *82*, 688. h) Zhuo, M. H.; Jiang, Y. J.; Fan, Y. S.; Gao, Y.; Liu, S.; Zhang, S. *Org. Lett.* **2014**, *16*, 1096. i) Sun, F. L.; Zheng, X. J.; Gu, Q.; He, Q. L.; You, S. L. *Eur. J. Org. Chem.* **2010**, 47. j) Li, Z.; Duan, Z.; Kang, J.; Wang, H.; Yu, L.; Wu, Y. *Tetrahedron*, **2008**, *64*, 1924. k) Wilsdorf, M.; Leichnitz, D.; Reissig, H. U. *Org. Lett.*, **2013**, *15*, 2494. l) Babu, B. M.; Thakur, P. B.; Rao, N. N.; Kumar, G. S.; Meshram, H. M. *Tetrahedron Lett.* **2014**, *55*, 1868. m) Rao, H. S. P.; Rao, A. V. B. *Beilstein J. Org. Chem.* **2016**, *12*, 496. n) Nambo, M.; Ariki, Z. T.; Gonzalez, D. C.; Beattie, D. D.; Crudden, C. M. *Org. Lett.* **2016**, *18*, 2339. o) Kumar, G. S.; Kumar, A. S.; Swetha, A.; Babu, B. M.; Meshram, H. M. *Synlett* **2016**, *27*, 631. p) Abbasabadi, K. M.; Baltork, I. M.; Tangestaninejad, S.; Moghadam, M.; Mirkhani, V.; Kia, R. *Tetrahedron* **2016**, *72*, 433.

6) a) Schick, J. W.; Crowley D. J. *J. Am. Chem. Soc.*, **1951**, *73*, 1377. b) Das, S. K.; Shagufta. Panda, G. *Tetrahedron Lett.* **2005**, *46*, 3097. c) Katritzky, A. R.; Toader, D. *J. Org. Chem.* **1997**, *62*, 4137. d) Chinta, B. S.; Baire, B. *Tetrahedron Lett.*, **2016**, *57*, 5381. e) Dong, C. P.; Kodama, S.; Uematsu, A.; Nomoto, A.; Ueshima, M.; Ogawa, A. *J. Org. Chem.* **2017**, *82*, 12530. f) Shen, X.; Gu, N.; Liu, P.; Ma, X.; Xie, J.; Liu, Y.; Dai, B. *Chin. J. Chem.* **2016**, *34*, 1033.

7) a) Miyaura, N.; Suzuki, A. *Chem. Rev.* **1995**, *95*, 2457. b) Suzuki, A. *J. Organomet. Chem.*, **1999**, *576*, 147. c) Phan, N. T. S.; Sluys, M. V. D.; Jones, C. W. *Adv. Synth. Catal.* **2006**, *348*, 609. d) Wolfe, J. P.; Singer, R. A.; Yang, B. H.; Buchwald, S. L. *J. Am. Chem. Soc.* **1999**, *121*, 9550. e) Molander, G. A.; Elia, M. D. *J. Org. Chem.* **2006**, *71*, 9198. f) Yu, J. Y.; Kuwano, R. *Org. Lett.* **2008**, *10*, 973. g) Lopez-Perez, A.; Adrio, J.; Carretero, J. C. *Org. Lett.* **2009**, *11*, 5514. h) Cao, L. L.; Li, X. N.; Meng, F. Y.; Jiang, G. F. *Tetrahedron Lett.* **2012**, *53*, 3873. i) Matthew, S. C.; Glasspoole, B. W.; Eisenberger, P.; Crudden, C. M. *J. Am. Chem. Soc.* **2014**, *136*, 5828. j) Nambo, M.; Crudden, C. M. *Angew. Chem. Int. Ed.* **2014**, *53*, 742.

8) a) Lyons, T. W.; Sanford, M. S. *Chem. Rev.* **2010**, *110*, 1147. b) Rouquet, R.; Chatani, N. *Angew. Chem. Int. Ed.* **2013**, *52*, 11726. c) Kakiuchi, F.; Chatani, N. *Adv. Synth. Catal.* **2003**, *345*, 1077. d) Niwa, T.; Yorimitsu, H.; Oshima, K. *Org. Lett.* **2007**, *9*, 2373. e) Song, G.; Su, Y.; Gong, X.; Han, K.; Li, X. *Org. Lett.* **2011**, *13*, 1968. f) Zhang, J.; Bellomo, A.; Creamer, A. D.; Dreher, S. D.; Walsh, P. J. *J. Am. Chem. Soc.* **2012**, *134*, 13765. g) Bellomo, A.; Zhang, J.; Trongsiriwat, N.; Walsh, P. J. *Chem. Sci.* **2013**, *4*, 849. h) Zhang, J.; Bellomo, A.; Trongsiriwat, N.; Jia, T.; Carroll, P. J.; Dreher, S. D.; Tudge, M. T.; Yin, H.; Robinson, J. R.; Schelter, E. J.; Walsh, P. J. *J. Am. Chem. Soc.* **2014**, *136*, 6276. i) Tabuchi, S.; Hirano, K.; Satoh, T.; Miura, M. *J. Org. Chem.* **2014**, *79*, 5401.

9) a) Tasker, S. Z.; Standley, E. A.; Jamison, T. F. *Nature* **2014**, *509*, 299. b) Saito, S.; Oh-tani, S.; Miyaura, N. *J. Org. Chem.* **1997**, *62*, 8024. c) Standley, E. A.; Tasker, S. Z.; Jensen, K. L.; Jamison, T. F. *Acc. Chem. Res.* **2015**, *48*, 1503. d) Zhang, C.; Tang, C.; Jiao, N. *Chem. Soc. Rev.* **2012**, *41*, 3464. e) Zhang, C.; Tanga, C.; Jiao, N. *Chem. Soc. Rev.*, **2012**, *41*, 3464. e) Correa, A.; Mancheno, O. G.; Bolm, C. *Chem. Soc. Rev.*, **2008**, *37*, 1108. f) Li, Y. Z.; Li, B. Z.; Lu, X. Y.; Lin, S.; Shi, Z. J. *Angew. Chem. Int. Ed.* **2009**, *48*, 3817. g) Zhao, X.; Wu, G.; Zhang, Y.; Wang, J. *J. Am. Chem. Soc.* **2011**, *133*, 3296. h) Cao, L. L.; Ye, Z. S.; Jiang, G. F.; Zhou, Y. G. *Adv. Synth. Catal.* **2011**, *353*, 3352. i) Taylor, B. L. H.; Harris, M. R.; Jarvo, E. R. *Angew. Chem. Int. Ed.* **2012**, *51*, 7790. j) Zhou, Q.; Srinivas, H. D.; Dasgupta, S.; Watson, M. P. *J. Am. Chem. Soc.* **2013**, *135*, 3307. k) Tobisu, M.; Yasutome, A.; Kinuta, H.; Nakamura, K.; Chatani, N. *Org. Lett.* **2014**, *16*, 5572. l) Sun, Y. Y.; Yi, J.; Lu, X.; Zhang, Z. Q.; Xiao, B.; Fu, Y. *Chem. Commun.*, **2014**, *50*, 11060.

10) a) Adamczyk, M.; Grote, J. *Org. Prep. Proced. Int.* **2001**, *33*, 95. b) Liu, C.; Mao, H.; Zheng, J.; Zhang, S. *J. Membr. Sci.* **2017**, *530*, 1. c) Cheltsov, M.; Aoyagi, A.; Aleshin, C. W.; Yu, T.; Gilliland, D.; Zhai, A.; Bobkov, J.; Reed, R.; Liddington. Abagyan, R. *J. Med. Chem.*, **2010**, *53*, 3899. d) Elam, C.; Lape, M.; Deye, J.; Zultowsky, J.; Stanton, D. T.; Paula, S. *Eur. J. Org. Chem.*, **2011**, *46*, 1512. e) Dibwe, D. F.; Awale, S.; Kadota, S.; Tezuka, Y. *Tetrahedron Lett.*, **2012**, *53*, 6186. f) Dibwe, D. F.; Awale, S.; Kadota, S.; Morita, H.; Tezuka, Y. *Tetrahedron Lett.*, **2014**, *55*, 1916. g) Yoshihara, H. A. I.; Apriletti, J. W.; Baxter, J. D.; Scanlana, T. S. *Bioorganic Med. Chem. Lett.*, **2001**, *11*, 2821. h) Joharapurkar, A. A.; Dhote, V. V.; Jain, M. R. *J. Med. Chem.* **2012**, *55*, 5649. i) Ohishi, T.; Kojima, T.; Matsuoka, T.; Shiro, M.; Kotsuki. H. *Tetrahedron Lett.*, **2001**, *42*, 2493. j) Liu, Y. L.; Liu, L.; Wang, Y. L.; Han, Y. C.; Wang. D.; Chen. Y. J. *Green Chem.* **2008**,

10, 635. k) Saha, S.; Alamsetti, S. K.; Schneider, C. *Chem. Commun.* **2015**, *51*, 1461. l) Dada, R.; Singh, G.; Pareek, A.; Kausar, S.; Yaragorla, S. *Tetrahedron Lett.* **2016**, *57*, 3739. m) Wang, Y.; Zhang, C.; Wang, H.; Jiang, Y.; Du, X.; Xu, D. *Adv. Synth. Catal.* **2017**, *359*, 791. n) Zhou, T.; Li, S.; Huang, B.; Li, C.; Zhao, Y.; Chen, J.; Chen, A.; Xiao, Y.; Liu, L.; Zhang, J. *Org. Biomol. Chem.*, **2017**, *15*, 4941.

11) a) Dubbaka, S. R.; Vogel, V. *Org. Lett.*, **2004**, *6*, 95. b) Collman, J. P.; Roper, W. R. *J. Am. Chem. Soc.* **1966**, *88*, 180. c) Kasahara, A.; Izumi, T.; Kudou, N.; Azami, H.; Yamamato, S. *Chem. Ind.* **1988**, 51. d) Miura, M.; Hashimoto, H.; Itoh, K.; Nomura, M. *Tetrahedron Lett.* **1989**, *30*, 975. e) Miura, M.; Hashimoto, H.; Itoh, K.; Nomura, M. *J. Chem. Soc. Perkin Trans.1* **1990**, *8*, 2207. f) Dubbaka, S. R.; Vogel, P. *J. Am. Chem. Soc.* **2003**, *125*, 15292. g) Dubbaka, S. R.; Vogel, P. *Tetrahedron Lett.*, **2006**, *47*, 3345. h) Zhao, X.; Dimitrijevic, E.; Dong, V. M. *J. Am. Chem. Soc.* **2009**, *131*, 3466. i) Zhang, M.; Zhang, S.; Lui, M.; Cheng, J. *Chem. Commun.*, **2011**, *47*, 11522. j) Yuan, K.; Doucet, H. *Chem. Sci.*, **2014**, *5*, 392. k) Yuan, K.; Sang, R.; Soule, J. F.; Doucet, H. *Catal. Sci. Technol.*, **2015**, *5*, 2904.

12) a) Villemin, D.; Hammadi, M.; Hachemi, M. *Synthetic Commun*., **2002**, *32*, 1501. b) Huang, L.; Zhao, J.; Guo, S.; Zhang, C.; Ma, J. *J. Org. Chem.* **2013**, *78*, 5627. b) Griffiths, J.; Wong-Yuncgh, K. U.; Awkin, C. J. C. S. *Chem. Comm*., **1976**, 676. c) Kim, H. Y.; Takizawa, S.; Oh, K. *Org. Biomol. Chem.*, **2016**, *14*, 7191. d) Suchard, O.; Kane, R.; Roe, B. J.; Zimmermann, E.; Jung, C.; Waske, P. A.; Mattaya, J.; Oelgemoller, M. *Tetrahedron*, **2006**, *62*, 1467. e) Uliana, M. P.; Vieira, Y. W.; Donatoni, M. C.; Correa, A. G.; Brocksom, U.; Brocksom, T. J. *J. Braz. Chem. Soc.*, **2008**, *19*, 1484.

13) a) Kita, Y.; Takeda, Y.; Okuno, T.; Egi, M.; Kawaguchi, K. I. K.; Akai, S. *Chem. Pharm. Bull.* **1997**, *45*, 1887. b) Stang, P. J.; Zhdan, V. V. *Chem. Rev.* **1996**, *96*, 1123.

14) a) Wang, H.; Ma, Y.; Tian, H.; Yu, A.; Chang, J.; Wu, Y. *Tetrahedron*, **2014**, *70*, 2669.

Chapter 3: Palladium-catalyzed *ortho*-arylation of D-(-)-2-phenylglycine methyl ester using bidentate picolinamide directing group

Introduction

Transition metal catalyzed C-H activation/functionalization is a well-known synthetic technique for C-C and C-hetero atom bond forming reactions and emerged as a reliable protocol to obtain functionalized small molecules.[1,2a-k] In this line, few reports described the transition metal-catalyzed bidentate directing group-assisted sp^2 and sp^3 C-H functionalization of amino acids and the synthesis of unnatural amino acid derivatives. Given the importance of amino acids in peptidomimetics, glycopeptide synthesis, protein engineering and drug discovery, the synthesis of unnatural amino acids considered as a valuable.[3a-d] Especially, the non-proteinogenic amino acids such as phenylglycine derivatives have unique structural properties and applications toward peptidomimetics and drug discovery (Figure 1).[4a-c] Phenylglycine derivatives have found applications in the synthesis of biologically active peptides or the natural products,[5,6] e.g., antibiotics, virginiamycin S,[5a-b] streptogramins B,[5c-d] pristinamycin I,[5e] dityromycin,[5f] β-lactam antibiotics,[5g] and anticancer activity[5h-l] and etc. Numerous methods been reported for the synthesis of phenylglycine unnatural amino acids.[7a-g,8]

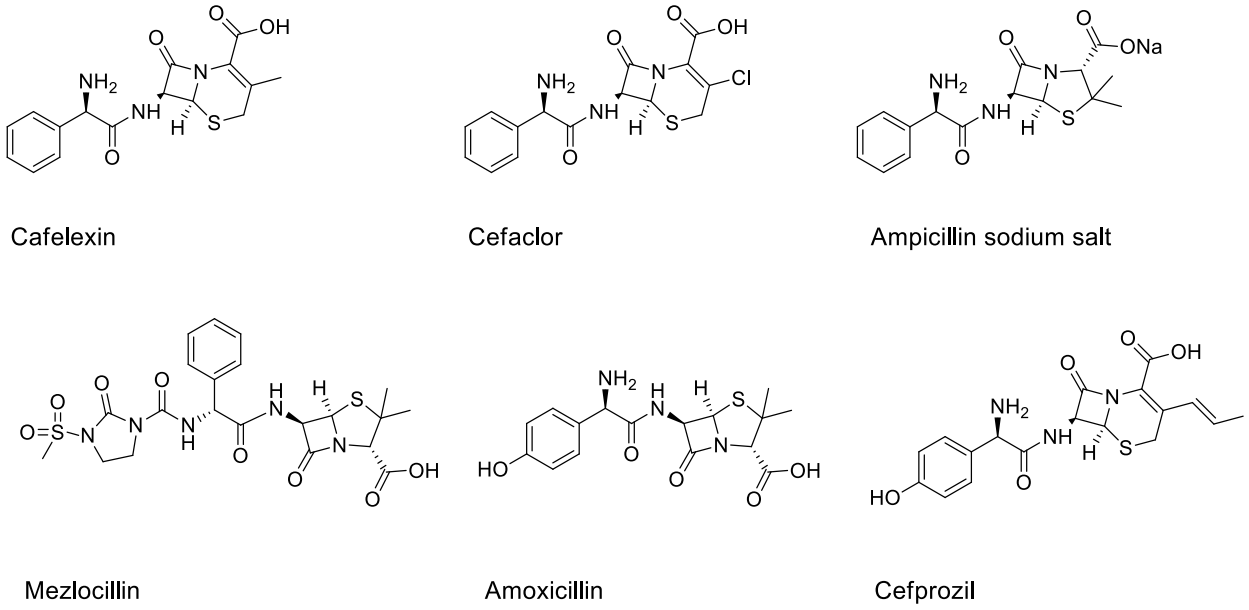
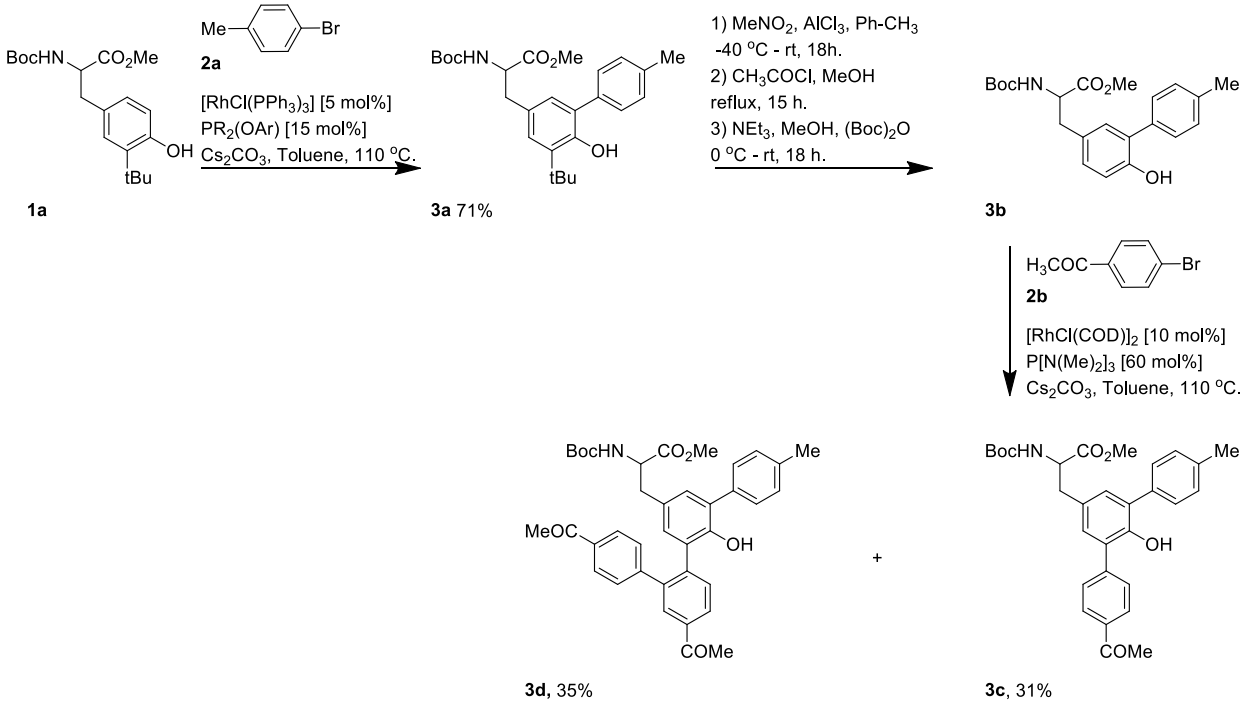


Figure 1. Representative examples of phenylglycine-based bio-active compounds

Given the pronounced biological activities and utility in organic synthesis, development of new methods for the synthesis of functionalized phenylglycine unnatural amino acid derivatives will

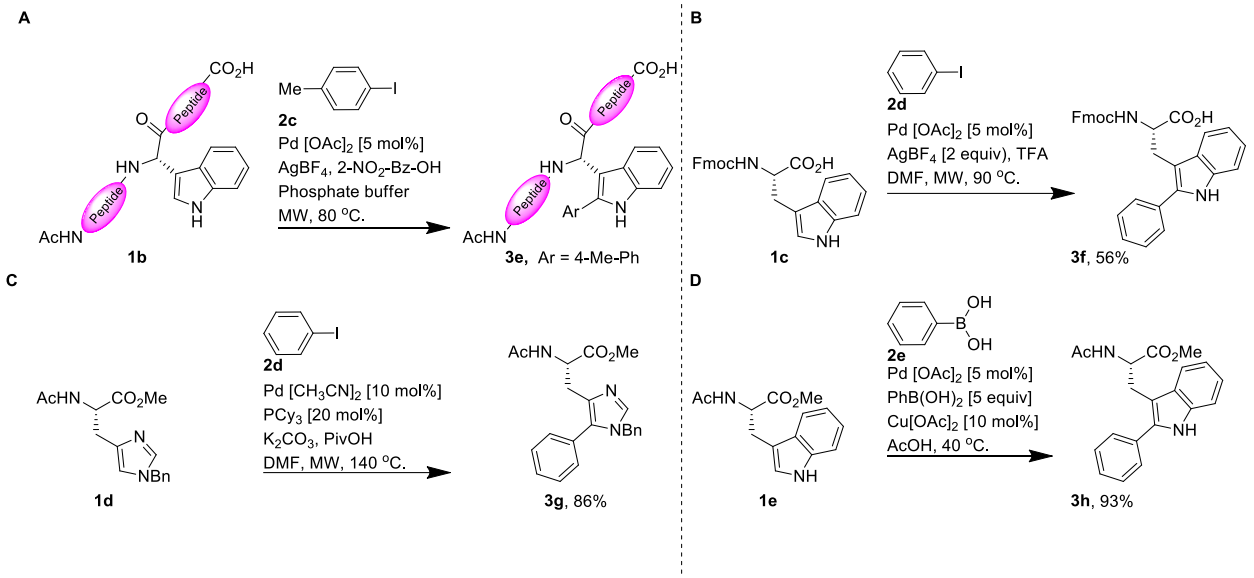
be appreciated.[1-9] A part of this thesis envisaged the synthesis of *ortho*- sp^2 C-H arylated phenylglycine derivatives via the transition metal-catalyzed bidentate directing group-assisted sp^2 C-H activation/functionalization of phenylglycine linked with picolinamide as the bidentate directing group. Some of the reports dealing with the functionalization of amino acids and the synthesis of unnatural amino acid derivatives via the transition metal-catalyzed bidentate directing group-assisted sp^2 and sp^3 C-H activation/functionalization are discussed here.



Scheme 1. Rhodium-catalyzed *ortho*-arylation tyrosine derivative.

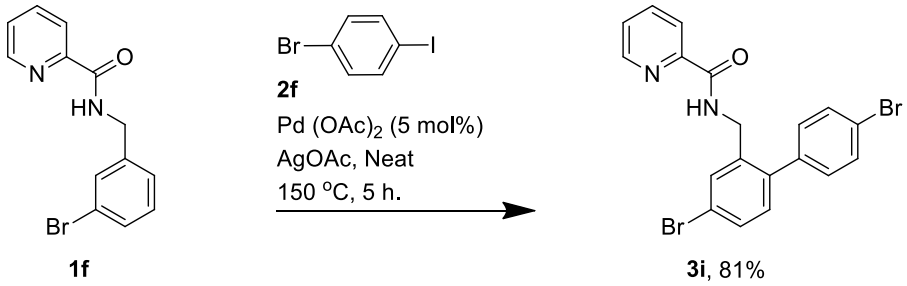
In 2009, Bedford and co-workers reported rhodium-catalyzed arylation of Boc-L-Tyr-OMe **1a** with aryl bromides (Scheme 1),[10a] which afforded monoarylated product **3a**. Further arylation of **3a** after removal of *t*-Bu group afforded **3c** led to the synthesis of arylated Boc-L-Tyr-OMe **3c** and **3d**. In 2010, Lavilla and co-workers reported selective arylation of tryptophan peptide (**1b**) with aryl iodide (**2c**), which afforded the arylated tryptophan peptide (**3e)** in moderate to good yields (Scheme 2A).[10b] In 2013, the same group also reported arylation at C-2 position of Fmoc-Trp-OH **1c** with aryl iodide **2d** under microwave irradiation, which afforded 2-aryl Fmoc-Trp-OH **3f** in 56% yield (Scheme 2B).[10c] In 2013, Rahul and co-workers reported palladium-catalyzed arylation at C-5 position of Ac-L-His-OMe **1d** using aryl iodide(s) **2d** as coupling partner, which resulted **3g** in 86% yield (Scheme 2C).[10d] In 2014, Fairlamb and co-workers reported mild reaction

condition for C-2 arylation of Ac-Trp-OMe **1e** and tryptophan peptides with aryl boronic acid(s) **2e** as coupling partner, which resulted **3h** in 93% yield (Scheme 2D).[10e]



Scheme 2. Palladium-catalyzed arylation of C(sp^2)-H bond in amino acids and peptides

Apart from the C(sp^2)-H arylation of amino acids, introduction other functional groups via transition metal-catalyzed reactions involving borylation,[10f-g] acetoxylation,[10h] halogenation and alkenylation[10i] were also reported.

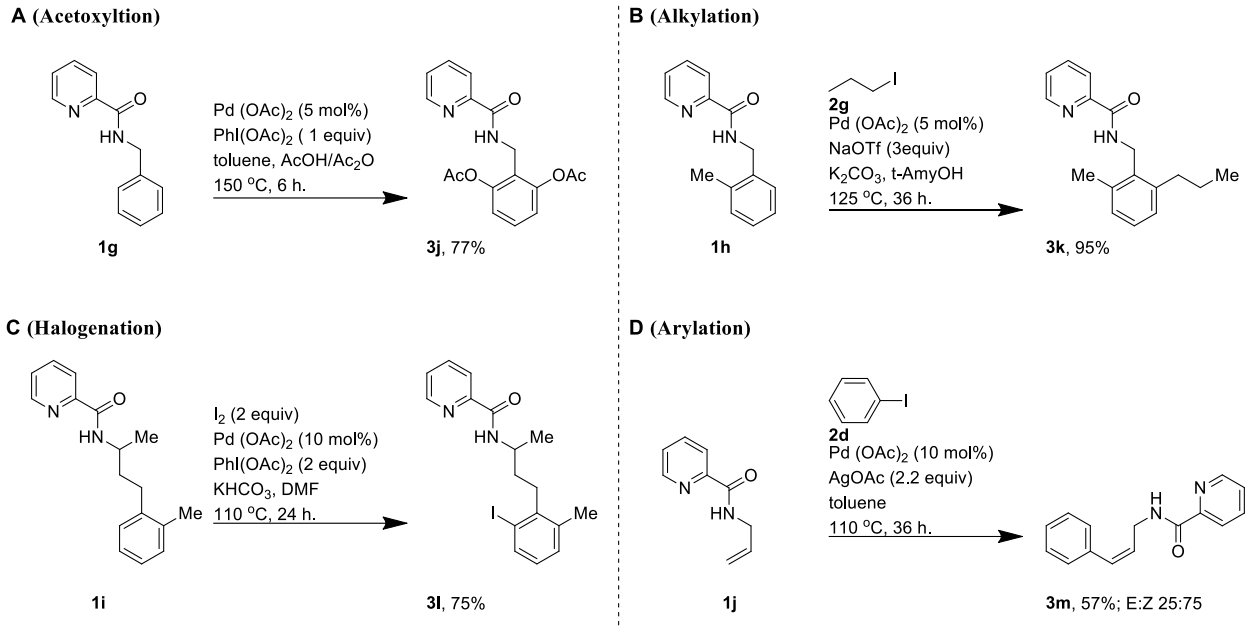


Scheme 3. Picolinamide-assisted C-H arylation of **1f**.

The first picolinamide assisted C-H functionalization was reported by Daugulis and co-workers in 2005 (Scheme 3)[11a] and the report described the arylation of C(sp^3)-H and C(sp^2)-H bonds with aryl iodides as coupling partner. The picolinamide **1f** with 4-bromoiodobenzene **2f** afforded *ortho*-arylated picolinamide **3i** in 81% yield. This paper also revealed the 8-aminoquinoline as the bidentate group for C(sp^3)-H arylation of carboxamides.

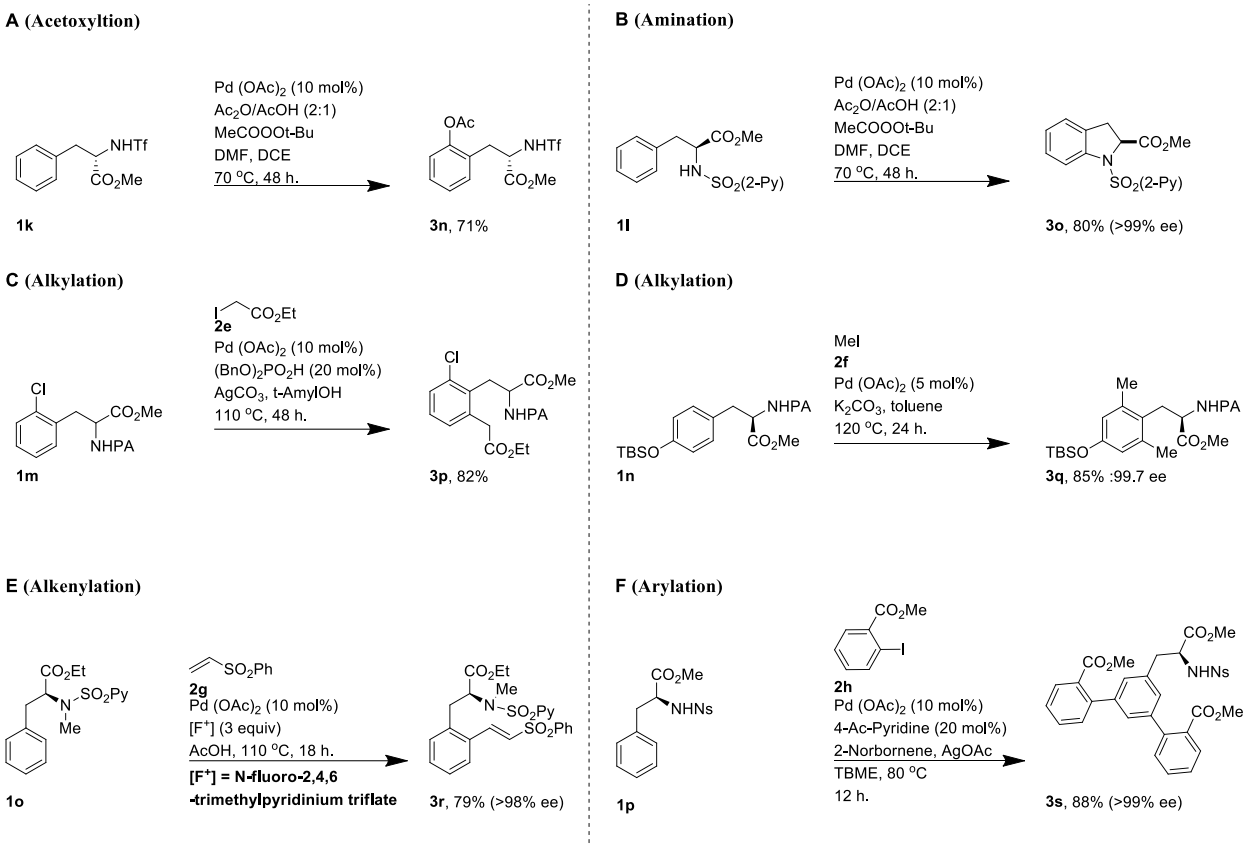
In 2009, Liang and co-workers reported Pd-catalyzed picolinamide and 8-aminoquinoline directed C(sp^2)-H acetoxylation (Scheme 4A).[11b] The picolinamide **1g** with $PhI(OAc)_2$ in presence of $AcOH/Ac_2O$ afforded bis-acetoxylated product **3j** in 77% yield. In 2013, Chen and co-workers

developed an efficient protocol for assembling *ortho*-alkylated aryls with the assistance of picolinamide (Scheme 4B).[11d] Recently, the same group reported *ortho*-iodination followed by cyclization to afford tetrahydroquinoline (Scheme 4C).[11e] Recently our group reported γ-arylation of allylamines assisted by picolinamide (Scheme 4D).[11f]

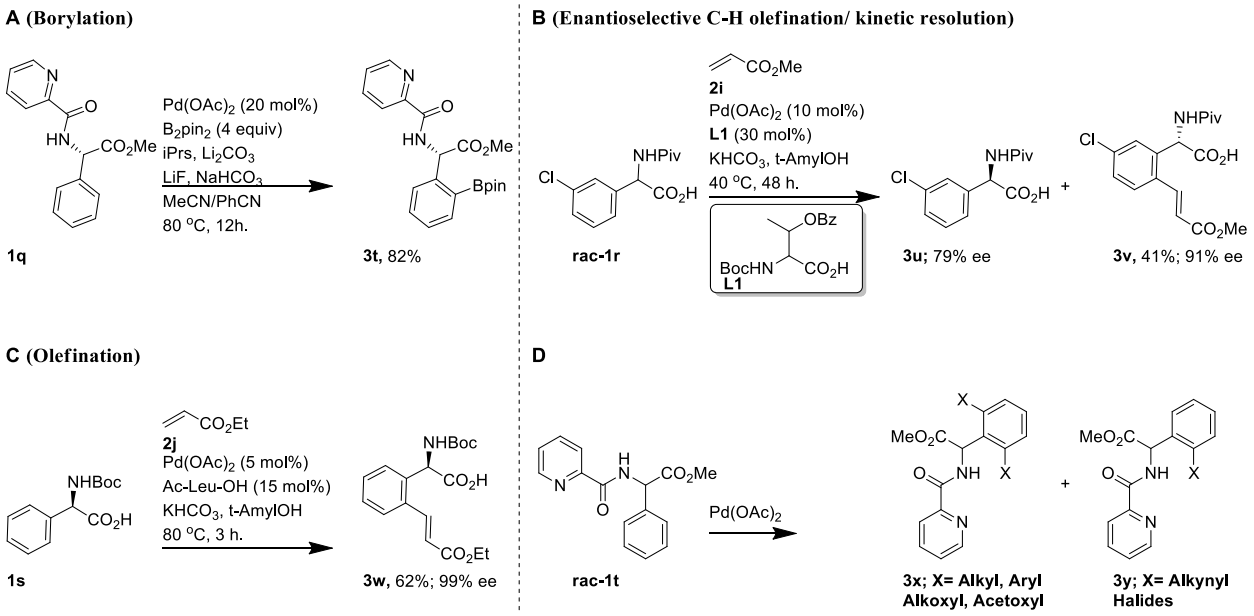


Scheme 4. Representative examples of Pd-catalyzed picolinamide-directed C(Sp^2)-H-functionalization.

In 2010, Yu and co-workers reported triflamide directed C(sp^2)-H acetoxylation of **1k**, which afforded the sp^2 C-H acetoxylated product **3n** (Scheme 5A).[12a] In 2013, the same group reported intramolecular amination of **1l**, which afforded chiral and achiral indolines (Scheme 5B).[12b] Chen and co-workers developed an efficient route for alkylation of unactivated C(sp^3)-H and *ortho* C-H bonds with the assistance picolinamide directing group (Scheme 5C).[12c] This work described few examples involving alkylation of phenylalanine and phenyl lycine derived picolinamides. Ma and co-workers reported *ortho*-alkylation of picolinamide derived from tyrosine **1n** with methyl iodide **2f** to afford bis-*ortho*-alkylated unnatural amino acid **3q** in 85% yield (Scheme 5D)[12d]. In 2015, Carretero and co-workers reported alkenylation of phenylalanine derivative **1o** with electron deficient alkene **2g**, which resulted *ortho*-alkenylated phenylalanine derivative **3r** in 79% yield (Scheme 5E)[12e]. Recently, Yu and co-workers developed remote C(sp^2)-H arylation of nosyl (Ns) protected phenylalanine derivative **1p** with aryl iodide(s) **2h**, which afforded bis-arylated phenylalanine derivatives **3s** in 88% yield (Scheme 5F).[12f]



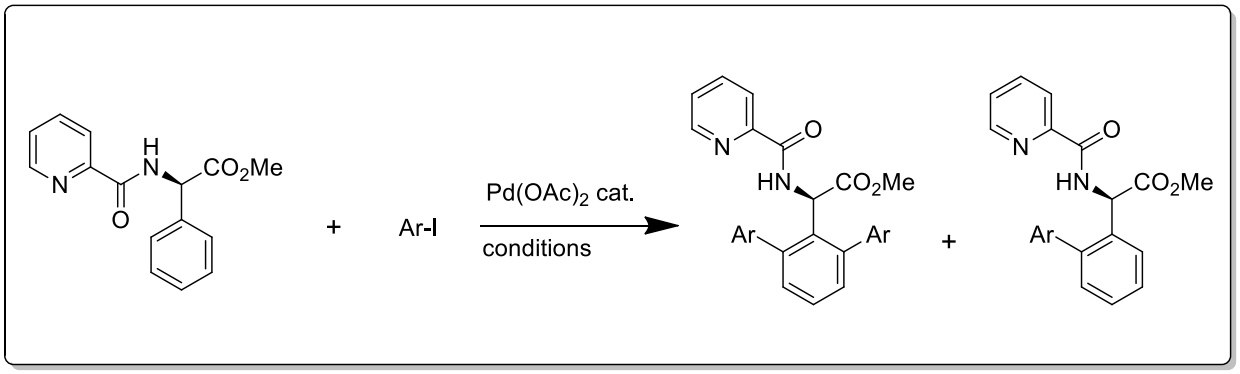
Scheme 5. Representative examples of Pd-catalyzed ligand directed C(sp^2)-H functionalization of amino acids.



Scheme 6. Pd-catalyzed C(sp^2)-H functionalization of phenylglycine derivatives

In 2014, Shi and co-workers reported picolinamide-assisted borylation of C(sp^3)-H and C(sp^2)-H bonds of amino acids and chiral amines (Scheme 6A).[13a] The reaction of picolinamide of phenylglycine **1q** with boronic ester B_2pin_2 afforded *ortho*-borylated product **3t** in 82 % yield. Recently, Yu and co-workers reported enantioselective olefination of racemic phenylglycine derivative using kinetic resolution method (Scheme 6B).[13c] Previously in 2015, the same group also developed an efficient protocol for *ortho*-C-H functionalization of phenylglycine and mandelic acid (Scheme 6C).[13b] For instance, the reaction of Boc-D-Phg-OH **1s** with electron deficient alkene **2j** afforded *ortho*-alkenyl product **3w** in 62% yield. During the course of investigation of the work shown in this Chapter, Jiang and co-workers reported bis-arylation, alkylation, alkoxylation and acetoxylation and mono-alkynylation, halogenation of rac-PA-Phg-OMe **rac-1t** (Scheme 6D).[13d] In 2017, Jiang and Zeng patented the work on *ortho*-C-H functionalization of D-(-)-phenylglycine methyl ester[13e]. Urriolabeitia and Co-workers reported the synthesis isoquinoline-1-carboxylates and isoindoline-1-carboxylates from racemic phenylglycine methyl ester[13f].

Given the importance of unnatural amino acids in general and phenylglycine derivatives in particular, in medicinal chemistry and utility in organic synthesis, synthesis of library of functionalized phenylglycine unnatural amino acid derivatives will be appreciated. With this motive, it was envisaged to investigate the Pd-catalyzed picolinamide-assisted *ortho*-arylation of D-(-)-phenylglycine methyl ester. Accordingly, a part of this thesis reports the synthesis of *ortho*-sp^2 C-H arylated D-(-)-phenylglycine methyl ester derivatives via the Pd-catalyzed picolinamide-assisted sp^2 C-H activation/functionalization of D-(-)-phenylglycine methyl ester (Scheme 7).

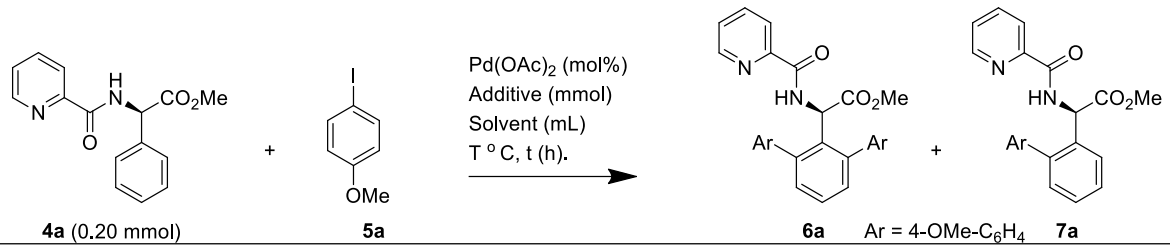


Scheme 7. This work. Pd-catalyzed picolinamide-assisted sp^2 C-H activation/functionalization of D-(-)-phenylglycine methyl ester.

Results and Discussion

At the outset, to identify efficient reaction conditions, optimization reactions were performed using D-(-)-phenylglycine methyl ester derived picolinamide (**4a**) (which was assembled from corresponding D-phenylglycine methyl ester and picolinic acid) with 4-methoxyiodobenzene (**5a**).

Table 1. Optimization of ortho-arylation of PA-D-Phg-OMe with 4-methoxy phenyl iodide[a]



4a (0.20 mmol) **5a** **6a** **7a**

Entry	Catalyst (5 mol%)	**5a** (mmol)	Additive (0.44 mmol)	Time (h)	Yield (%) **6a**	**7a**
1	$Pd(OAc)_2$	0.80	AgOAc	24	23	29
2	$Pd(OAc)_2$	0.30	AgOAc	24	20	-
3	$Pd(OAc)_2$	0.80	AgOAc	42	72	8
4[b]	$Pd(OAc)_2$	0.80	AgOAc	42	72	8
5[b]	$Pd(OAc)_2$	0.80	AgOAc	48	75	10
6	$PdCl_2$	0.80	AgOAc	42	60	18
7	$Pd(OAc)_2$	0.60	AgOAc	42	59	33
8	$Pd(OAc)_2$	0.80	Ag_2CO_3	42	22	0
9	$Pd(OAc)_2$	0.80	KOAc	42	68	0
10[c]	$Pd(OAc)_2$	0.80	AgOAc	42	16	45
11[d]	$Pd(OAc)_2$	0.80	AgOAc	42	0	40
12[e]	$Pd(OAc)_2$	0.80	AgOAc	42	32	42

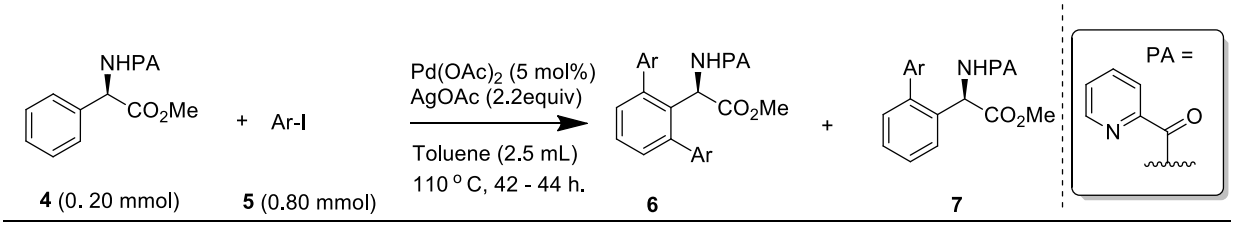
[a] Conditions: **4a** (0.20 mmol), **5a** (0.80 mmol), $Pd(OAc)_2$ (5 mol%), AgOAc (0.44 mmol), Toluene (2.5 mL), at 110 °C, 42-44h. [b] $Pd(OAc)_2$ (10 mol%), [c] DCE, [d] *t*-BuOH, [e] *t*-Amyl-OH used as solvent.

Heating picolinamide **4a** (0.2 mmol) and aryl iodide **5a** (0.8 mmol) with 5 mol% of $Pd(OAc)_2$, and 0.44 mmol of AgOAc at 110 °C afforded the C-H arylated phenylglycine derivative **6a** (bis-*ortho*-arylated product) in 23% yield and **7a** (mono-*ortho*-arylated product) in 29% yield (Table 1, entry 1). Next, the same reaction using 0.3 mmol of aryl iodide resulted only bis-arylated product **6a** in 20% yield (Table 1, entry 2). Increasing reaction period to 42 h resulted bis-*ortho*-arylated product

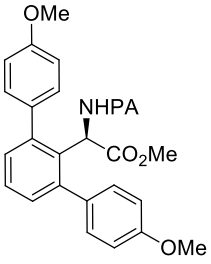
6a in 72 % yield and **7a** in 8% yield (Table 1, entry 3). Similar results were observed when employing 10 mol% of $Pd(OAc)_2$ (Table 1, entry 4) and increasing reaction period to 48 h (Table 1, entry 5). Next, usage of other Pd(II) catalyst such as $PdCl_2$ resulted 60% of **6a** and 18% of **7a** (Table 1, entry 6). Next, the reaction using 0.6 mmol of aryl iodide resulted only bis-arylated product **6a** in 59% yield and mono-aryl product (**7a**) in 33% yield (Table 1, entry 7). Usage of other additives, such as Ag_2CO_3 and KOAc afforded the product **6a** in 22 and 68% yields (Table 1, entries 8 and 9). The Pd-catalyzed arylation of **4a** with **5a** in other solvents, such as DCE, *t*-BuOH, *t*-Amyl-OH were not fruitful and convincing than the other better results obtained (Table 1, entries 10-12).

Having done the optimization of reaction conditions, then it was envisaged to investigate the scope and generality of this reaction by using various aryl iodides possessing electron-donating and electron-withdrawing groups (Table 2). Accordingly, the Pd(II)-catalyzed reactions of picolinamide **4a** and aryl iodides containing electron-donating groups at the *para* or *meta* position afforded the corresponding bis-*ortho* C-H arylated phenylglycine derivatives **6a-e** in 56-79% yields and in one of the cases, the mono-*ortho*-arylated product **7b** was obtained in 33% yield (Table 2). Then, the Pd(II)-catalyzed reaction of picolinamide **4a** and 6-iodo-2,3-dihydrobenzo[*b*][1,4]dioxine gave the bis-*ortho* C-H arylated phenylglycine derivatives **6f** in 76% yield. Next, the Pd(II)-catalyzed reactions of picolinamide **4a** and aryl iodides containing electron-withdrawing groups at the *para* or *meta* position or PhI furnished the corresponding bis-*ortho* C-H arylated phenylglycine derivatives **6g-m** in 51-85% yields. The Pd(II)-catalyzed reaction of picolinamide **4a** and aryl iodides containing CF_3 groups afforded the corresponding bis-*ortho* C-H arylated phenylglycine derivatives **6n-o** in 40-50% yields. Furthermore, the Pd(II)-catalyzed reaction of picolinamide **4a** and aryl iodides containing useful functional groups such as Ac or COOMe and disubstituted aryl iodides were also afforded the corresponding bis-*ortho* C-H arylated phenylglycine derivatives **6p-t** in 22-80% yields. Notably, in some of these reactions the corresponding mono-*ortho*-arylated products **7c-e** were also obtained in 24-52% yields (Table 2). Notably, the bis-*ortho* C-H arylated phenylglycine derivative **6u** (28%) was also obtained from the corresponding Pd(II)-catalyzed reaction of picolinamide **4a** with bis iodo compound. It is to be noted that while the Pd(II)-catalyzed reactions of picolinamide **4a** with the corresponding aryl iodides gave the corresponding bis-*ortho* C-H arylated phenylglycine derivatives **6**, in some cases only the mono *ortho* C-H arylated phenylglycine derivatives **7** were obtained depending on the

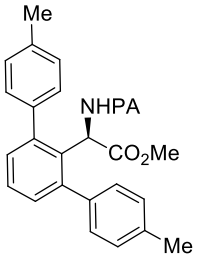
Table 2. Pd-catalyzed picolinamide-assisted sp^2 C-H arylation of D-(-)-phenylglycine methyl ester **4** with different aryl iodides.



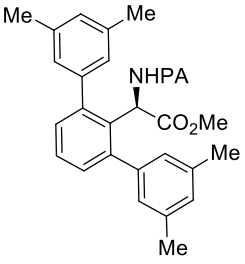
4 (0. 20 mmol) **5** (0.80 mmol) **6** **7**



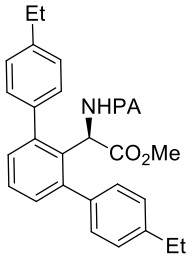
6a, 72% ; **7a** (mono), 10%



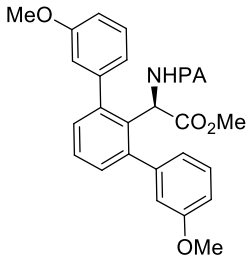
6b, 78%



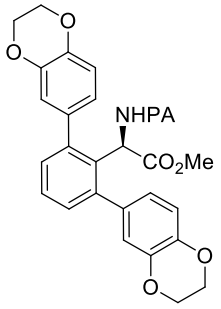
6c, 79%



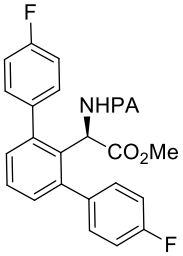
6d, 78%



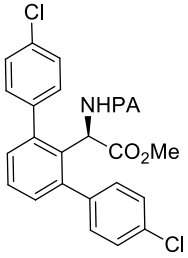
6e, 56% ;
7b (Mono), 33%



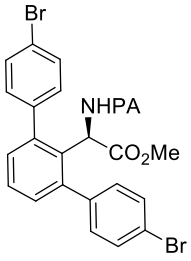
6f, 76%



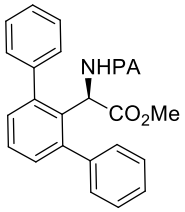
6g, 51%



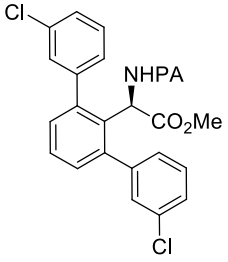
6h, 51%



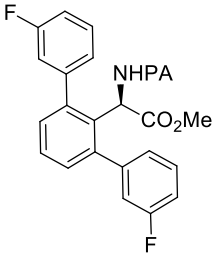
6i, 60%



6j, 85%



6k, 68%

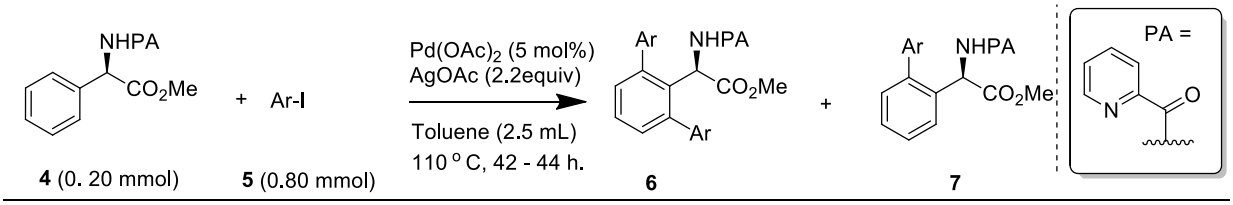


6l, 76%

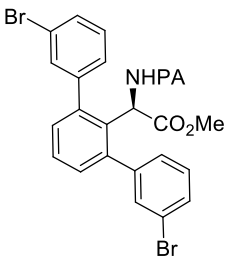
substituent present in the aryl iodides. While it cannot be generalized, however, the reactions involving aryl iodides containing *meta* substituent gave the mono *ortho* C-H arylated phenylglycine derivatives **7** in addition to the bis-*ortho* C-H arylated phenylglycine derivatives **6**. While an exact reason is not clear at this stage, perhaps the reactions involving aryl iodides

containing *meta* substituent might be slow and hence, the corresponding reactions afforded both **6** and **7**.

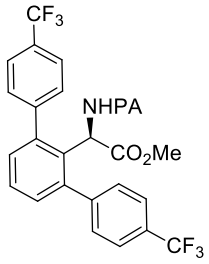
Table 2 (continued). Pd-catalyzed picolinamide-assisted sp^2 C-H arylation of D-(-)-phenylglycine methyl ester **4** with different aryl iodides.



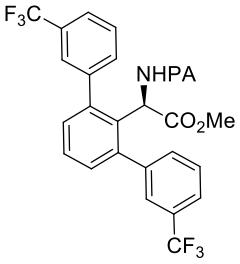
4 (0. 20 mmol) **5** (0.80 mmol) **6** **7**



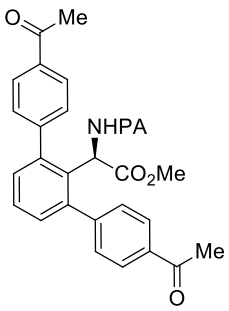
6m, 52%



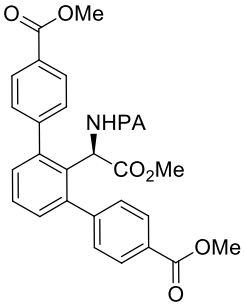
6n, 40%



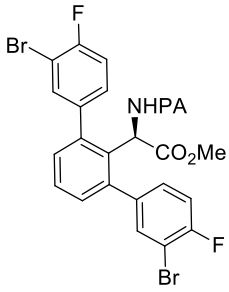
6o, 50%



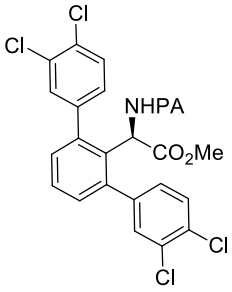
6p, 80%



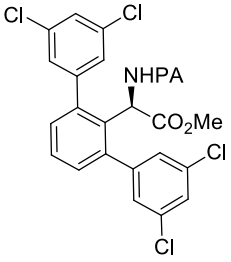
6q, 64%



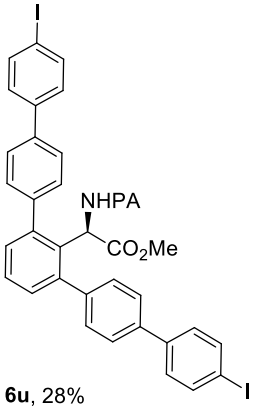
6r, 28% :
7c (mono), 48%



6s, 64% :
7d (mono), 24%



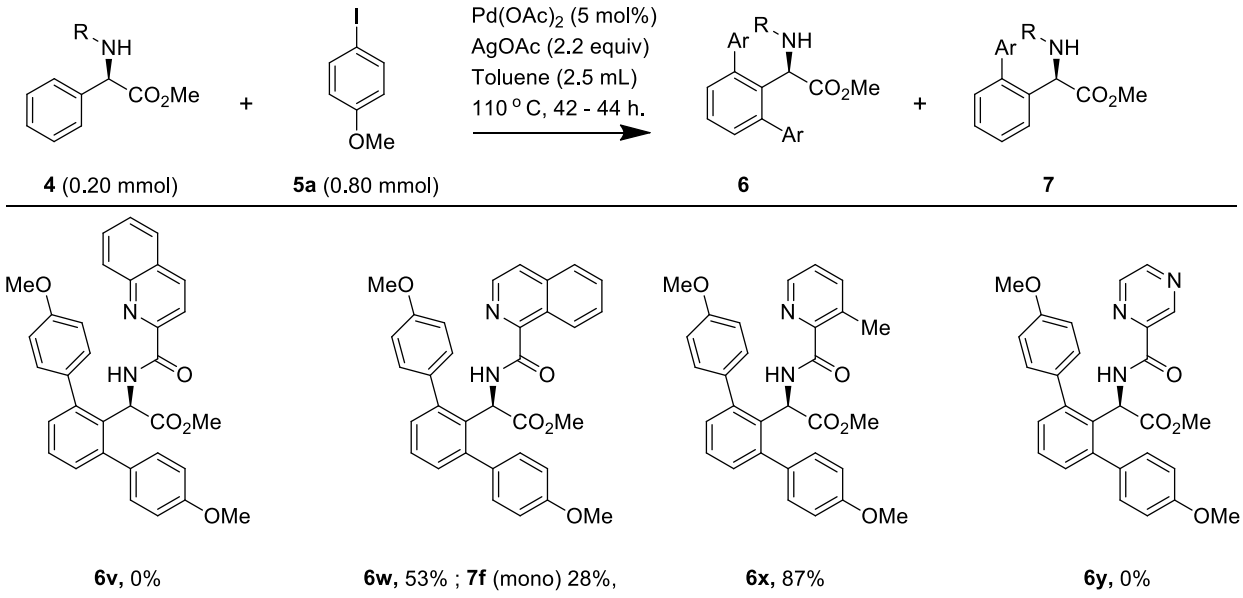
6t, 22% :
7e (mono), 52%



6u, 28%

Having done the arylation of D-phenylglycine methyl ester **4a** using picolinamide as the bidentate directing group, then it was envisaged to investigate the scope of arylation of D-phenylglycine methyl ester by linking with different bidentate directing groups. Accordingly, various amides **4b-e** of D-phenylglycine methyl ester linked with different bidentate directing groups were assembled. Acid chlorides, of quinoline-2-carboxylic acid, isoquinoline-1-carboxylic acid, 3-methyl picolinic acid and pyrazine-2- carboxylic acid were treated with D-phenylglycine methyl ester to assemble the corresponding amides **4b-e**. Subsequently, these amides were subjected to the Pd(II)-catalyzed arylation with **5a** (Table 3). C-H arylated products **6w**, **7f** and **6x** were obtained from their corresponding amides. These results indicated that isoquinoline-1-carboxamide and 3-methyl-

Table 3. Scope of bidentate directing groups in the Pd(II)-catalyzed sp^2 C-H arylation of D-(-)-phenylglycine methyl ester **4** with **5a**.[a]



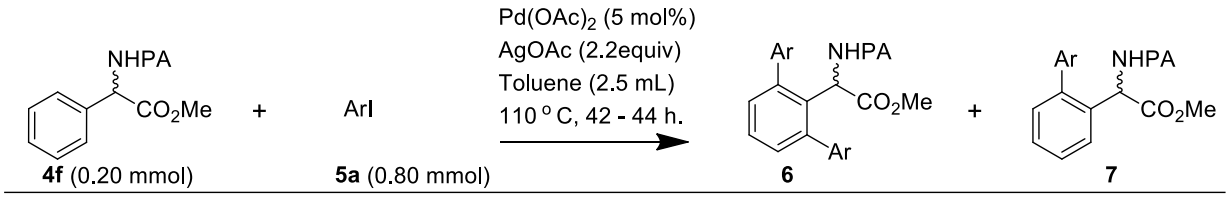
[a] Reactions were done using the corresponding amides **4b-e** of D-phenylglycine methyl ester linked with the corresponding different bidentate directing groups (carboxylic acids).

picolinamide have served as the directing groups similar to picolinamide. Accordingly, C-H arylated products **6w**, **7f** and **6x** were obtained from the Pd(II)-catalyzed arylation of their corresponding amides **4c** and **4d** with **5a** (Table 3). On the other hand, the expected C-H arylated products **6v** and **6y** were not obtained from their corresponding amides. These results indicated that quinoline-2-carboxamide and pyrazine-2-carboxamide did not serve as the directing groups

and hence, C-H arylated products **6v** and **6y** were not obtained from the Pd(II)-catalyzed arylation of their corresponding amides **4b** and **4e** with **5a**.

After investigating the arylation of D-phenylglycine methyl ester **4a** using picolinamide as the bidentate directing group, subsequently, the Pd(II)-catalyzed picolinamide-directed arylation of rac-phenylglycine methyl ester **4f** with aryl iodides such as **5a** and 4-acetyliodobenzene were performed, which afforded the bis-*ortho* C-H arylated, rac-phenylglycine derivatives **6z** and **6aa**

Table 4. Pd(II)-catalyzed sp^2 C-H arylation of rac-phenylglycine methyl ester **4f** with **5a**.



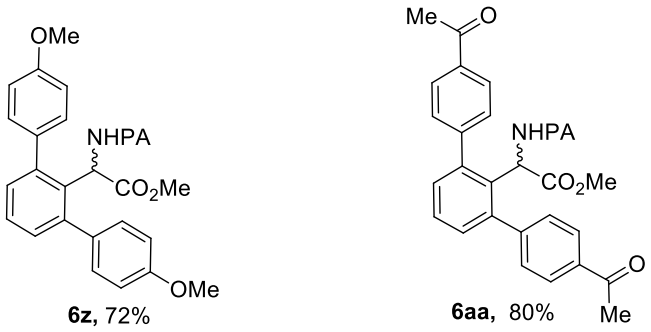
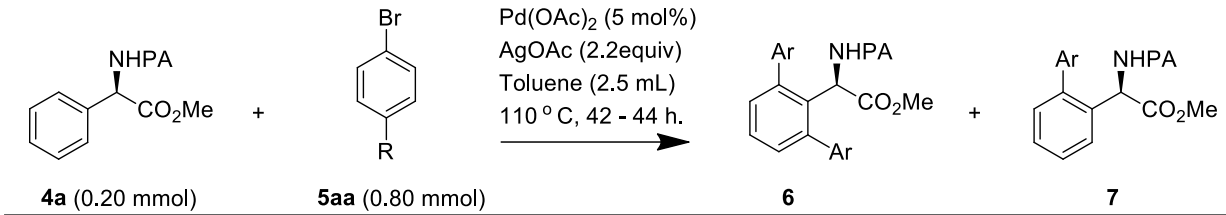
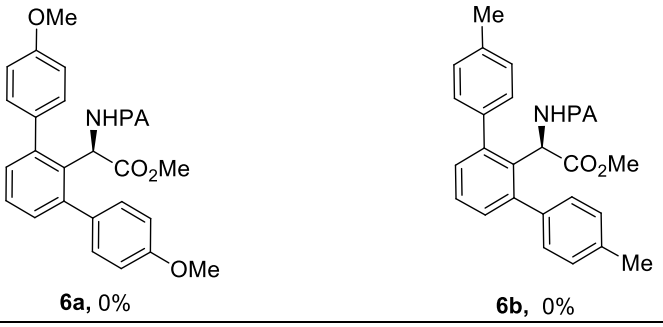


Table 5. Pd(II)-catalyzed sp^2 C-H arylation of phenylglycine methyl ester **4a** with aryl bromides.

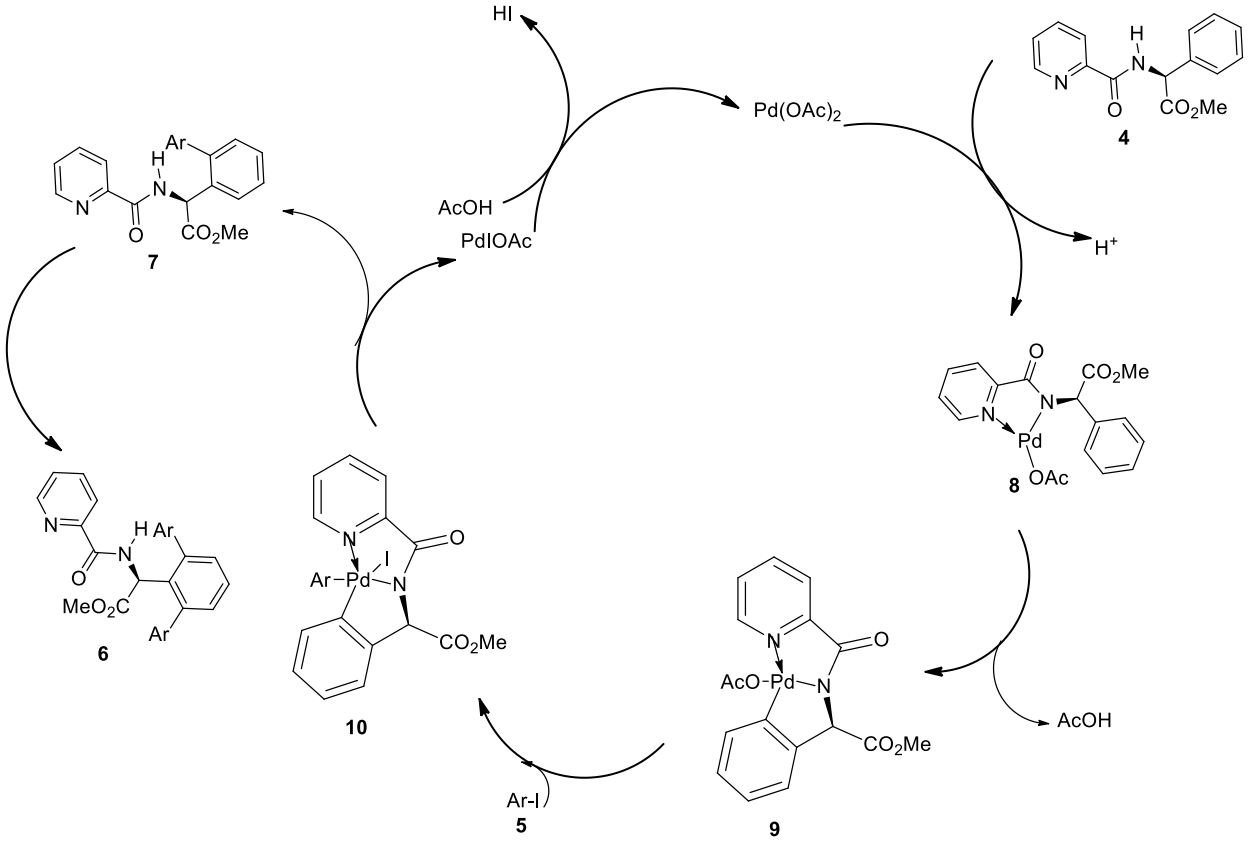




in 72-80% yields (Table 4) (During the course of investigation of the work shown in this Chapter, Jiang and co-workers reported bis-arylation, rac-PA-Phg-OMe **rac-1t** (Scheme 6D).[13d]

Given that the Pd-catalyzed, picolinamide-directed arylations of D-phenylglycine methyl ester were carried using aryl iodides as coupling partners (Tables 1-4), trials were also made to use aryl bromides (Table 5). However, the Pd-catalyzed, picolinamide-directed arylations of D-phenylglycine methyl ester with aryl bromides were not fruitful (Table 5).

The plausible mechanism of picolinamide-directed ortho-arylation of D-(-)-phenylglycine methyl ester described in scheme 8. The first step involves bidentate co-ordination of Pd-catalyst with substrate **4**. Next, the C-H activation at proximal C-H bond affords the transition state **9**, which further undergoes oxidative addition with aryl iodide provides Pd(IV) species **10**. Then the reductive elimination gives the mono *ortho*- arylated product **7**. Next, the repetition of process from **8**-**10** with the product **7** affords the bis-*ortho*-arylated product **6**.

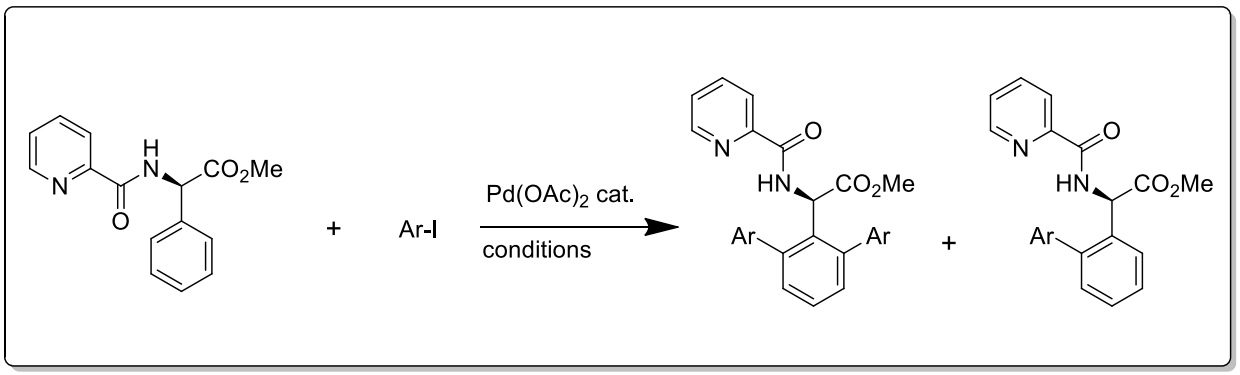


Scheme 8. Plausible mechanism of *ortho*- arylation.

Summary

In summary, Chapter 3 reported the investigations on the Pd(II)-catalyzed bidentate directing group picolinamide-assisted sp^2 C-H activation/arylation of D-(-)-phenylglycine methyl ester and the synthesis of various *ortho*-sp^2 C-H arylated D-(-)-phenylglycine methyl ester derivatives in good to high yields. Given the importance of phenylglycine derivatives in medicinal chemistry,

the synthesis of *ortho*-sp^2 C-H arylated D-(-)-phenylglycine methyl ester derivatives shown in this work is a contribution to the library of unnatural amino acids. Given that during the course of investigation of the work shown in this Chapter, Jiang and co-workers reported[13d] the bis-arylation, phenylglycine methyl ester, further scope and generality could not be established at this stage.



General. Melting points are uncorrected. IR spectra of compounds were recorded as thin films or KBr pellets using Perkin Elmer FT-IR spectrometer. ^1H and ^{13}C NMR spectra of compounds were recorded on Bruker 400 MHz and 100 MHz spectrometers respectively using TMS as an internal standard. Mass spectra were recorded using SYNAPT G2S High Definition Mass Spectrometer. Column chromatography was carried out using silica gel 100-200 mesh. Reactions were performed in anhydrous solvent under a nitrogen atmosphere. Solutions were dried using anhydrous Na_2SO_4. Thin layer chromatography analysis was performed on silica gel plates and components were visualized by observation under iodine. Isolated yields of all the compounds were reported.

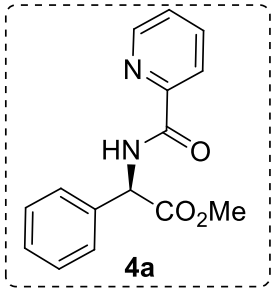
General Procedure for preparation of amide 4a-f.

To a solution of picolinic acid (10 mmol) in dry dichloromethane (30 mL), 1-hydroxy benzotriazole hydrate (11 mmol), and 1,3-dicyclohexylcarbodiimide (11 mmol) were added at 0 ^oC under nitrogen atmosphere. The suspension was warmed to room temperature and stirred for 1 h. Then, D-(-)-α-phenylglycine (10 mmol) was added and mixture was stirred for 12 -15 h at room temperature. After this period, the resulting suspension was filtered through celite, extracted with chloroform (3x20 mL), and washed with brine solution. Then the filtrate was evaporated. The crude reaction mixture was purified by silica gel column (100-200 mesh, eluent; EtOAc: hexane) to afford the corresponding picolinamides **4a-f**.

General Procedure for Palladium-Catalyzed *ortho*-Arylation of D-(-)-2-Phenylglycine Methyl Ester.

To an oven dried round bottom flask (*R*)-methyl 2-phenyl-2-(picolinamido) acetate (0.2 mmol), $Pd(OAc)_2$ (5 mol %), iodo benzene (4.0 equiv, 0.80 mmol), AgOAc (2.2 equiv) in anhydrous toluene (2.5 mL) were added. The suspension was heated at 110 ^oC for 40 - 44 h under nitrogen atmosphere. After the reaction period, the reaction mixture was diluted with EtOAc and concentrated under reduced pressure and purification of the resulting reaction mixture by column chromatography silica gel furnished the corresponding bis-arylated (*R*)-methyl 2-phenyl-2-(picolinamido) acetates **6a-6aa**.

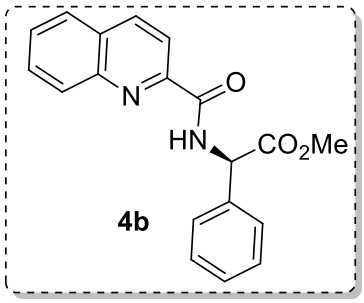
(*R*)-Methyl 2-phenyl-2-(picolinamido)acetate (4a): Following the general procedure, **4a** was



4a

obtained after purification by column chromatography on silica gel (EtOAc:hexane = 40:60); Rf = 0.5 (EtOAc : Hex = 30:70); as a brown solid; yield: 53% (715mg) ; mp 70-72 ^oC ; IR (KBr): 3386, 3061, 2953, 1745, 1680, 1510 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 8.97 (d, 1H, *J* = 7.0 Hz), 8.61-8.60 (m, 1H), 8.18 (d, 1H, *J* = 7.8 Hz), 7.85 (td, 1H, J_1 = 7.7 Hz, J_2 = 1.6 Hz), 7.51 – 7.35 (m, 6H), 5.79 (d, 1H, *J* = 7.5 Hz), 3.79 (s, 3H) ; ^{13}C NMR (100 MHz, $CDCl_3$): δ 171.1, 163.8, 149.2, 148.3, 137.3, 136.5, 129.0, 128.6, 127.4, 126.5, 122.4, 56.6, 52.9 ; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{15}H_{15}N_2O_3$: 271.1083; found 271.1093.

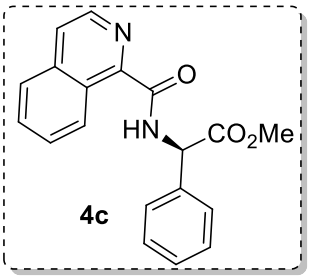
(*R*)-Methyl 2-phenyl-2-(quinoline-2-carboxamido)acetate (4b): Following the general



4b

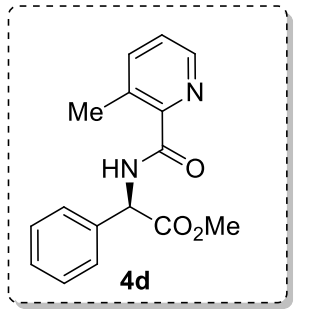
procedure, **4b** was obtained after purification by column chromatography on silica gel (EtOAc:hexane = 40:60); Rf = 0.6 (EtOAc : Hex = 30:70); as a colorless solid; yield: 47% (745mg) ; mp 118-120 ^oC ; IR (KBr): 3383, 2954, 2857, 1745, 1681, 1518 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 9.19 (d, 1H, *J* = 7.1 Hz), 8.30 (dd, 2H, J_1 = 15.6 Hz, J_2 = 8.5 Hz), 8.19 (d, 1H, *J* = 8.5 Hz), 7.89 (d, 1H, *J* = 8.2 Hz), 7.79 (t, 1H, *J* = 7.1 Hz), 7.66-7.63 (m, 1H), 7.56 (d, 2H, *J* = 7.4 Hz), 7.45 – 7.36 (m, 3H), 5.87 (d, 1H, *J* = 7,5 Hz), 3.82 (s, 3H) ; ^{13}C NMR (100 MHz, $CDCl_3$): δ 171.3, 164.1, 149.0, 146.6, 137.5, 136.5, 130.2, 130.0, 129.4, 129.1, 128.7, 128.1, 127.7, 127.5, 118.8, 56.8, 52.9; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{19}H_{17}N_2O_3$: 321.1239; found 321.1227.

(*R*)-Methyl 2-(isoquinoline-1-carboxamido)-2-phenylacetate (4c): Following the general procedure, **4c** was obtained after purification by column chromatography on silica gel (EtOAc:hexane = 35:65); Rf = 0.6 (EtOAc : Hex = 30:70); as a colorless solid; yield: 50% (784mg) ; mp 100-102 ^{o}C ; IR (KBr): 3383, 3054, 2849, 1744, 1674, 1505 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.59 (t, 1H, *J* = 8.5 Hz), 9.24 (s, 1H), 8.56 – 8.52 (m, 1H), 7.89 – 7.28 (m, 9H), 5.87-5.83 (m, 1H), 3.83 (d, 3H, *J* = 8.9 Hz) ; ^{13}C NMR (100 MHz, $CDCl_3$): δ 171.3, 165.5, 147.2, 140.4, 137.4, 137.4, 136.6, 130.5, 129.1, 128.8, 128.61, 128.60, 127.7, 127.5, 127.1, 126.8, 124.7, 56.84, 56.83, 52.9; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{19}H_{17}N_2O_3$: 321.1239; found 321.1254.



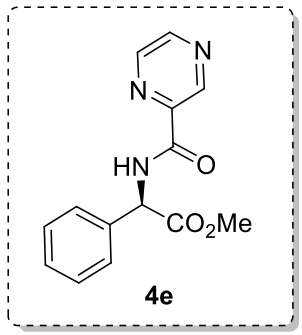
4c

(*R*)-Methyl 2-(3-methylpicolinamido)-2-phenylacetate (4d): Following the general procedure, **4d** was obtained after purification by column chromatography on silica gel (EtOAc:hexane = 30:70); Rf = 0.7 (EtOAc : Hex = 30:70); as a colorless solid; yield: 55% (781mg) ; mp 75-77 ^{o}C ; IR (KBr): 3387, 3039, 2950, 1745, 1679, 1497 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.11 (d, 1H, *J* = 6.6 Hz), 8.44 (d, 1H, *J* = 4.3 Hz), 7.58 (d, 1H, *J* = 7.7 Hz), 7.51 (d, 2H, *J* = 7.6 Hz), 7.42 – 7.28 (m, 4H), 5.74 (d, 1H, *J* = 7.4 Hz), 3.78 (s, 3H), 2.72 (s, 3H) ; ^{13}C NMR (100 MHz, $CDCl_3$): δ 171.4, 165.4, 146.4, 145.7, 140.8, 136.7, 135.7, 129.0, 128.5, 127.4, 126.0, 56.6, 52.8, 20.5; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{16}H_{17}N_2O_3$: 285.1239; found 285.1227.



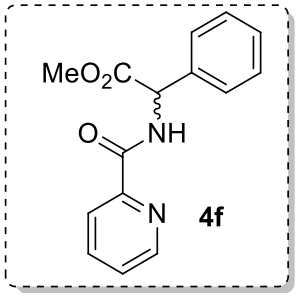
4d

(*R*)-Methyl 2-phenyl-2-(pyrazine-2-carboxamido)acetate (4e): Following the general procedure, **4e** was obtained after purification by column chromatography on silica gel (EtOAc:hexane = 60:40); Rf = 0.3 (EtOAc : Hex = 30:70); as a brown semi solid; yield: 54% (744mg) ; IR (KBr): 3390, 2953, 2853, 1745, 1680, 1515 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.38 (d, 1H, *J* = 1.1 Hz), 8.78 (d, 1H, *J*= 2.4 Hz), 8.74 (d, 1H, *J* = 6.8 Hz), 8.58 (d, 1H, *J*=1.5 Hz), 7.49 – 7.37 (m, 5H), 5.79 (d, 1H, *J* = 7.4 Hz), 3.8 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.9, 162.5, 147.6, 144.5, 144.0, 142.8, 136.1, 129.1, 128.8, 127.4, 56.5, 53.0; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{14}H_{14}N_3O_3$: 272.1035; found 272.1028.

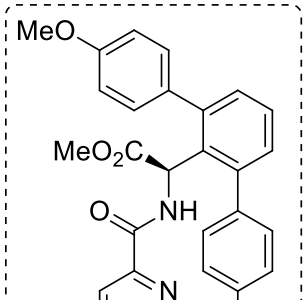


4e

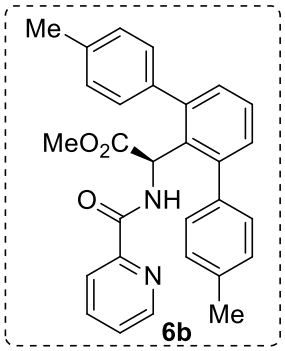
Methyl 2-phenyl-2-(picolinamido)acetate (4f): Following the general procedure, **4f** was obtained after purification by column chromatography on silica gel (EtOAc:hexane = 40:60); Rf = 0.5 (EtOAc : Hex = 30:70); as a brown solid; yield: 53% (715 mg) ; mp 98-100 ^{o}C ; IR (KBr): 3387, 3062, 2961, 1745, 1680, 1510 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.97 (d, 1H, *J* = 6.8 Hz), 8.60 (d, 1H, *J* = 4.5 Hz), 8.17 (d, 1H, *J* = 7.8 Hz), 7.85 (t, 1H, *J* = 7.7 Hz), 7.51 – 7.35 (m, 6H), 5.80 (d, 1H, *J* = 7.5 Hz), 3.79 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 171.1, 163.8, 149.2, 148.3, 137.3, 136.5, 129.0, 128.6, 127.4, 126.5, 122.4, 56.6, 52.9 ; HRMS (ESI): *m/z* [M + H]$^{+}$ calcd for $C_{15}H_{15}N_2O_3$: 271.1083; found 271.1071.



(*R*)-Methyl 2-(4,4''-dimethoxy-[1,1':3',1''-terphenyl]-2'-yl)-2-(picolinamido)acetate (6a): Following the general procedure, **6a** was obtained after purification by column chromatography on silica gel (EtOAc:hexane = 60:40); Rf = 0.4 (EtOAc : Hex = 30:70); as a colorless solid; yield: 72% (69 mg) ; mp 150-152 ^{o}C ; IR (KBr): 3375, 2952, 2836, 1745, 1680, 1610 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.52 (d, 1H, *J* = 4.6 Hz), 8.45 (d, 1H, *J* = 8.6 Hz), 8.06 (d, 1H, *J* = 7.8 Hz), 7.77 (td, 1H, J_1 = 7.7 Hz, J_2 = 1.5 Hz), 7.40 – 7.35 (m, 6H), 7.25 (d, 2H, *J* = 7.6 Hz), 7.00 (d, 4H, *J* = 8.8 Hz), 6.18 (d, 1H, *J* = 8.7 Hz), 3.88 (s, 6H), 3.65 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 171.5, 162.9, 159.1, 149.5, 148.0, 142.7, 137.1, 133.9, 133.4, 130.7, 130.4, 127.4, 126.1, 122.2, 113.6, 55.3, 52.9, 52.6; HRMS (ESI): *m/z* [M + H]$^{+}$ calcd for $C_{29}H_{27}N_2O_5$: 483.1920; found 483.1904

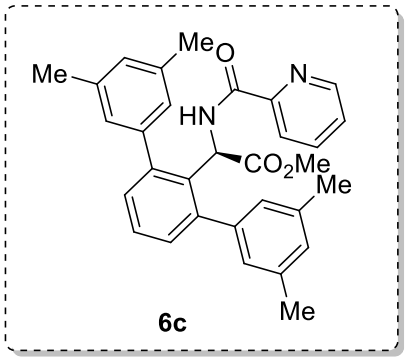


(*R*)-Methyl 2-(4,4''-dimethyl-[1,1':3',1''-terphenyl]-2'-yl)-2-(picolinamido)acetate (6b): Following the general procedure, **6b** was obtained after purification by column chromatography on silica gel (EtOAc:hexane = 40:60); Rf = 0.6 (EtOAc : Hex = 30:70); as a colorless solid; yield: 78% (70 mg) ; mp 131-133 ^{o}C ; IR (KBr): 3382, 3027, 2946, 1747, 1682, 1512 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.52 (d, 1H, *J* = 4.6 Hz), 8.44 (d, 1H, *J* = 8.6 Hz), 8.07 (d, 1H, *J* = 7.8 Hz), 7.77 (td, 1H, J_1 = 7.7 Hz, J_2 = 1.4 Hz), 7.40 – 7.27 (m, 12H), 6.16 (d, 1H, *J* = 8.8 Hz), 3.63 (s, 3H), 2.46 (s, 6H) ; ^{13}C NMR (100 MHz, $CDCl_3$): δ 171.5, 162.9, 149.5, 147.9, 143.0, 138.1, 137.3, 137.0, 133.5, 130.2,



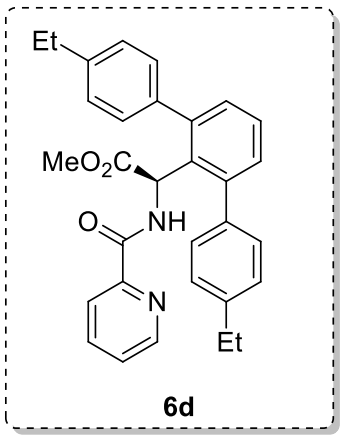
129.5, 128.9, 127.4, 126.0, 122.2, 52.9, 52.6, 21.4; HRMS (ESI): *m/z* [M + H]$^+$ calcd for $C_{29}H_{27}N_2O_3$: 451.2022; found 451.2040.

(*R*)-Methyl 2-(picolinamido)-2-(3,3'',5,5''-tetramethyl-[1,1':3',1''-terphenyl]-2'-yl)acetate (6c): Following the general procedure, **6c** was obtained after purification by column chromatography on silica gel (EtOAc:hexane = 25:75); Rf = 0.7 (EtOAc : Hex = 30:70); as a colorless solid; yield: 79% (76 mg) ; mp 168-170 ^oC ; IR (KBr): 3379, 3023, 2950, 1747, 1682, 1507 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.57 (d, 1H, *J* = 4.2 Hz), 8.52 (d, 1H, *J* = 8.9 Hz), 8.11 (d, 1H, *J* = 7.8 Hz), 7.79 (td, 1H, J_1 = 7.7 Hz, J_2 = 1.7 Hz), 7.42 – 7.38 (m, 2H), 7.30-7.28 (m, 1H), 7.09 (s, 6H), 6.19 (d, 1H, *J* = 9.0 Hz), 3.62 (s, 3H), 2.41 (s, 12H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 171.5, 162.8, 149.8, 148.0, 143.3, 140.8, 137.7, 137.0, 133.1, 129.8, 129.3, 127.5, 127.3, 126.0, 122.4, 52.8, 52.4, 21.4; HRMS (ESI): *m/z* [M + H]$^+$ calcd for $C_{31}H_{31}N_2O_3$: 479.2335; found 479.2346.



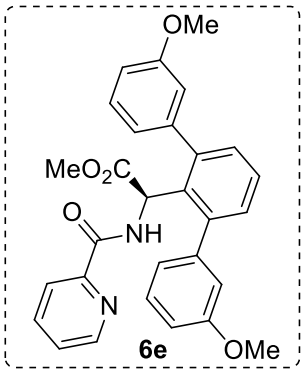
6c

(*R*)-Methyl 2-(4,4''-diethyl-[1,1':3',1''-terphenyl]-2'-yl)-2-(picolinamido)acetate (6d): Following the general procedure, **6d** was obtained after purification by column chromatography on silica gel (EtOAc:hexane = 25:75); Rf = 0.8 (EtOAc : Hex = 30:70); as a colorless solid; yield: 78% (74 mg) ; IR (KBr): 3376, 3035, 2964, 1745, 1682, 1510 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.49 (d, 1H, *J* = 4.6 Hz), 8.40 (d, 1H, *J* = 8.5 Hz), 8.05 (d, 1H, *J* = 7.8 Hz), 7.77 (td, 1H, J_1 = 7.6 Hz, J_2 = 1.4 Hz), 7.40 – 7.26 (m, 12H), 6.16 (d, 1H, *J* = 8.7 Hz), 3.62 (s, 3H), 2.75 (q, 4H, *J* = 7.6 Hz), 1.32 (t, 6H, *J* = 7.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 171.5, 162.9, 149.5, 147.9, 143.5, 143.0, 138.3, 137.0, 133.5, 130.2, 129.5, 127.7, 127.4, 126.0, 122.2, 53.0, 52.6, 28.7, 15.5; HRMS (ESI): *m/z* [M + H]$^+$ calcd for $C_{31}H_{31}N_2O_3$: 479.2335; found 479.2341.



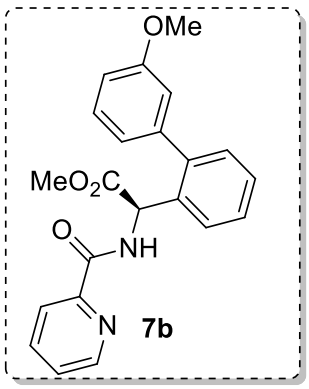
6d

(*R*)-Methyl 2-(3,3''-dimethoxy-[1,1':3',1''-terphenyl]-2'-yl)-2-(picolinamido)acetate (6e): Following the general procedure, **6e** was obtained after purification by column chromatography on silica gel (EtOAc:hexane = 55:45); Rf = 0.3 (EtOAc : Hex = 30:70); as a colorless solid; yield: 56% (54 mg) ; mp 98-100 ^oC ; IR (KBr): 3372, 3062, 2838, 1741, 1680, 1508 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.49 (d, 1H, *J* = 4.4 Hz), 8.40 (d, 1H, *J* = 8.4 Hz), 8.05 (d, 1H, *J* = 7.8 Hz), 7.78

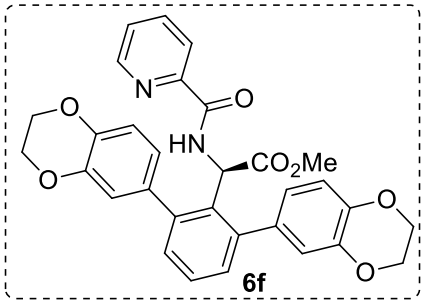


– 7.75 (m, 1H), 7.42 – 7.35 (m, 4H), 7.30 – 7.28 (m, 1H), 6.99 – 6.97 (m, 6H), 6.18 (d, 1H, *J* = 8.8 Hz), 3.81 (s, 6H), 3.65 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 171.5, 162.8, 159.3, 149.4, 148.0, 142.9, 142.2, 137.0, 133.1, 130.1, 129.3, 127.4, 126.1, 122.2, 121.9, 114.9, 113.8, 55.1, 52.9, 52.7 ; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{29}H_{27}N_2O_3$: 483.1920; found 483.1901.

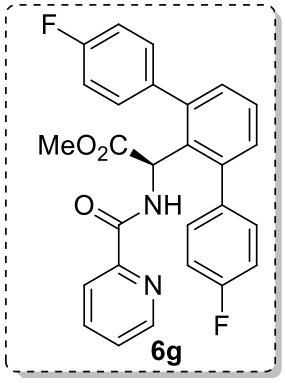
(*R*)-Methyl 2-(3'-methoxy-[1,1'-biphenyl]-2-yl)-2-(picolinamido)acetate (7b): Following the general procedure, **7b** was obtained after purification by column chromatography on silica gel (EtOAc:hexane = 65:35); Rf = 0.4 (EtOAc : Hex = 30:70); as a colorless solid; yield: 33% (25 mg) ; IR (KBr): 3374, 3054, 2951, 1747, 1681, 1588 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.78 (d, 1H, *J* = 5.8 Hz), 8.59 (d, 1H, *J* = 4.5 Hz), 8.14 (d, 1H, *J* = 7.8 Hz), 7.85 – 7.81 (m, 1H), 7.60 – 7.57 (m, 1H), 7.46 – 7.34 (m, 5H), 7.09 – 7.08 (m, 2H), 6.97 – 6.95 (m, 1H), 5.89 (d, 1H, *J* = 6.9 Hz), 3.84 (s, 3H), 3.72 (s, 3H) ; ^{13}C NMR (100 MHz, $CDCl_3$): δ 171.5, 163.6, 159.3, 149.3, 148.2, 142.5, 141.5, 137.3, 134.2, 130.7, 129.4, 128.4, 128.2, 127.2, 126.4, 122.3, 121.9, 114.9, 113.6, 55.2, 53.8, 52.8 ; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{22}H_{21}N_2O_4$: 377.1501; found 377.1515.



(*R*)-Methyl 2-(2,6-bis(2,3-dihydrobenzo[b][1,4]dioxin-6-yl)phenyl)-2-(picolinamido)acetate (6f): Following the general procedure, **6f** was obtained after purification by column chromatography on silica gel (EtOAc:hexane = 75:25); Rf = 0.1 (EtOAc : Hex = 30:70); as a colorless solid; yield: 76% (82mg) ; mp 125-127 ºC ; IR (KBr): 3381, 3077, 2954, 1744, 1679, 1509 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.54 – 8.48 (m, 2H), 8.05 (d, 1H, *J* = 7.7 Hz), 7.77 (t, 1H, *J* = 7.7 Hz), 7.39 – 7.23 (m, 4H), 6.95 – 6.90 (m, 6H), 6.20 (d, 1H, *J* = 8.8 Hz), 4.33 (s, 8H), 3.69 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 171.6, 162.9, 149.5, 148.0, 143.2, 143.2, 142.4, 137.0, 134.2, 133.7, 130.2, 127.3, 126.0, 122.8, 122.2, 118.7, 117.0, 64.42, 64.38, 52.8, 52.7.

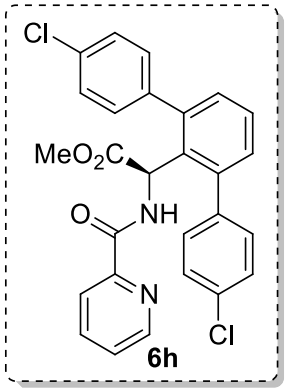


(*R*)-Methyl 2-(4,4''-difluoro-[1,1':3',1''-terphenyl]-2'-yl)-2-(picolinamido)acetate (6g): Following the general procedure, **6g** was obtained after purification by column chromatography



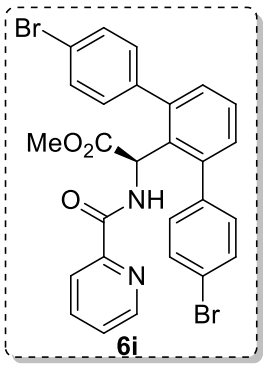
on silica gel (EtOAc:hexane = 30:70); Rf = 0.6 (EtOAc : Hex = 30:70); as a colorless solid; yield: 51% (47mg) ; mp 77-79 ^{o}C ; IR (KBr): 3379, 3050, 2954, 1745, 1681, 1510 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.52 (d, 1H, *J* = 4.6 Hz), 8.37 (d, 1H, *J* = 8.2 Hz), 8.04 (d, 1H, *J* = 7.8 Hz), 7.79 (t, 1H, *J* = 7.8 Hz),7.43 – 7.37 (m, 6H), 7.25 (d, 2H, *J* = 7.6 Hz), 7.14 (t, 4H, *J* = 8.6 Hz), 6.04 (d, 1H, *J* = 8.2 Hz), 3.65 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 171.3, 162.8, 162.4 (d, *J* = 240 Hz), 149.2, 148.0, 142.1, 137.1, 136.8 (d, *J* = 3.4 Hz), 133.7, 131.3, (d, *J* = 7.7 Hz), 130.5, 127.5, 126.2, 115.1 (d, *J* = 21.2 Hz), 52.9, 52.8 ; HRMS (ESI): *m/z* [M + H]$^{+}$ calcd for $C_{27}H_{21}F_2N_2O_3$: 459.1520; found 459.1505.

(*R*)-methyl 2-(4,4''-dichloro-[1,1':3',1''-terphenyl]-2'-yl)-2-(picolinamido)acetate (6h):



Following the general procedure, **6h** was obtained after purification by column chromatography on silica gel (EtOAc:hexane = 30:70); Rf = 0.7 (EtOAc : Hex = 30:70); as a colorless solid; yield: 51% (50 mg) ; mp 170-172 ^{o}C ; IR (KBr): 3385, 3062, 2950, 1743, 1680, 1509 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.53 (d, 1H, *J* = 4.2 Hz), 8.35 (d, 1H, *J* = 8.2 Hz), 8.03 (d, 1H, *J* = 7.8 Hz), 7.79 (td, 1H, J_1 = 7.7 Hz, J_2 = 1.6 Hz), 7.43 – 7.34 (m, 10H), 7.23 (d, 2H, *J* = 7.6 Hz), 6.02 (d, 1H, *J* = 8.2 Hz), 3.67 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 171.2, 162.8, 149.1, 148.1, 141.9, 139.3, 137.1, 133.8, 133.3, 130.9, 130.5, 128.4, 127.6, 126.3, 122.0, 53.0, 52.9; HRMS (ESI): *m/z* [M + H]$^{+}$ calcd for $C_{27}H_{21}Cl_2N_2O_3$: 491.0929; found 491.0911.

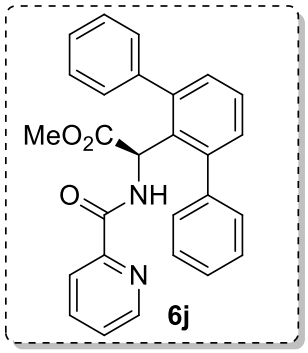
(*R*)-Methyl 2-(4,4''-dibromo-[1,1':3',1''-terphenyl]-2'-yl)-2-(picolinamido)acetate (6i):



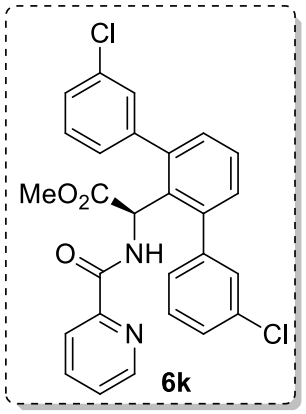
Following the general procedure, **6i** was obtained after purification by column chromatography on silica gel (EtOAc:hexane = 30:70); Rf = 0.7 (EtOAc : Hex = 30:70); as a colorless solid; yield: 60% (70mg) ; mp 171-172 ^{o}C ; IR (KBr): 3391, 3054, 2957, 1743, 1680, 1508 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.54 – 8.53 (m, 1H), 8.34 (d, 1H, *J* = 8.1 Hz), 8.03 (d, 1H, *J* = 7.8 Hz), 7.79 (td, 1H, J_1 = 7.7 Hz, J_2 = 1.7 Hz), 7.58 (d, 4H, *J* = 8.2 Hz), 7.43 – 7.37 (m, 2H), 7.29 (d, 4H, *J* = 8.6 Hz), 7.23 (d, 2H, *J* = 7.6 Hz), 6.02 (d, 1H, *J* = 8.1 Hz), 3.67 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 171.2, 162.8, 149.1,

148.1, 141.8, 139.8, 137.1, 133.2, 131.3, 131.2, 130.4, 127.6, 126.3, 122.0, 53.0, 52.8; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{27}H_{21}Br_2N_2O_3$: 578.9919; found 578.9943.

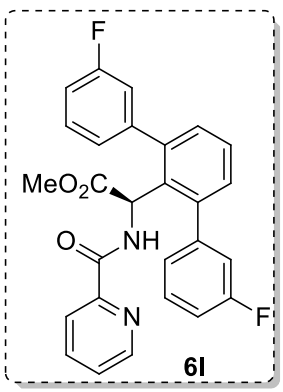
(*R*)-Methyl 2-([1,1':3',1''-terphenyl]-2'-yl)-2-(picolinamido)acetate (6j): Following the general procedure, **6j** was obtained after purification by column chromatography on silica gel (EtOAc:hexane = 35:65); Rf = 0.5 (EtOAc : Hex = 30:70); as an oily liquid; yield: 85% (71 mg) ; IR (KBr): 3379, 3056, 2950, 1744, 1681, 1508 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 8.52 – 8.51 (m, 1H), 8.41 (d, 1H, *J* = 8.1 Hz), 8.06 (dd, 1H, J_1= 7.8 Hz, J_2= 0.8 Hz), 7.79 – 7.75 (m, 1H), 7.46 – 7.39 (m, 13H), 7.31 – 7.29 (m, 1H), 6.13 (d, 1H, *J*= 8.6 Hz), 3.63 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 171.4, 162.8, 149.4, 148.0, 143.1, 141.0, 137.0, 133.3, 130.2, 129.6, 128.2, 127.7, 127.4, 126.1, 122.2, 52.9, 52.6 ; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{27}H_{23}N_2O_3$: 423.1709; found 423.1723.



(*R*)-Methyl 2-(3,3''-dichloro-[1,1':3',1''-terphenyl]-2'-yl)-2-(picolinamido)acetate (6k): Following the general procedure, **6k** was obtained after purification by column chromatography on silica gel (EtOAc:hexane = 30:70); Rf = 0.6 (EtOAc : Hex = 30:70); yield: 68% (67mg) ; as an oily liquid ; IR (KBr): 3380, 3058, 2951, 1744, 1681, 1508 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 8.57 (d, 1H, *J* = 3.6 Hz), 8.39 (d, 1H, *J* = 8.2 Hz), 8.04 (d, 1H, *J* = 7.8 Hz), 7.78 (td, 1H, J_1 = 7.7 Hz, J_2 = 1.7 Hz), 7.44 – 7.25 (m, 12H), 6.01 (d, 1H, *J* = 8.4 Hz), 3.71 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 171.2, 162.9, 149.1, 142.5, 141.7, 137.1, 134.1, 133.3, 130.4, 129.9, 129.4, 128.0, 127.8, 127.6, 126.2, 122.1, 52.9, 52.8; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{27}H_{21}Cl_2N_2O_3$: 491.0929; found 491.0910.

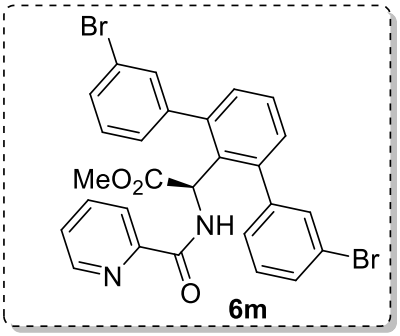


(*R*)-Methyl 2-(3,3''-difluoro-[1,1':3',1''-terphenyl]-2'-yl)-2-(picolinamido)acetate (6l): Following the general procedure, **6l** was obtained after purification by column chromatography on silica gel (EtOAc:hexane = 35:65); Rf = 0.6 (EtOAc : Hex = 30:70); as an oily liquid; yield: 76% (70mg) ; IR (KBr): 3380, 3060, 2953, 1745, 1682, 1581, 1510 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 8.53 (d, 1H, *J* = 4.6 Hz), 8.40 (d, 1H, *J* = 8.4 Hz), 8.04 (d, 1H, *J* = 7.8 Hz), 7.79-7.76 (m, 1H), 7.46 – 7.38 (m, 4H), 7.28 – 7.13 (m, 8H), 6.07 (d, 1H, *J* = 8.5 Hz), 3.69 (s, 3H) ; ^{13}C NMR (100 MHz, $CDCl_3$): δ



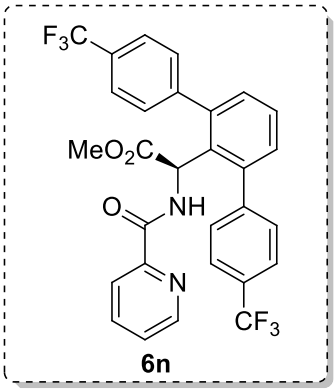
171.3, 162.9, 162.5 (d, *J* = 246 Hz), 149.1, 148.1, 142.9 (d, *J* = 7.7 Hz), 141.7 (d, *J* = 1.2 Hz), 137.1, 133.3, 130.3, 129.7 (d, *J* = 8.5 Hz), 127.6, 126.2, 125.4, 122.1, 116.9 (d, *J* = 21.4 Hz), 114.7 (d, *J* = 20.7 Hz), 52.8, 52.8; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{27}H_{21}F_2N_2O_3$: 459.1520; found: 459.1502.

(*R*)-Methyl 2-(3,3''-dibromo-[1,1':3',1''-terphenyl]-2'-yl)-2-(picolinamido)acetate(6m):



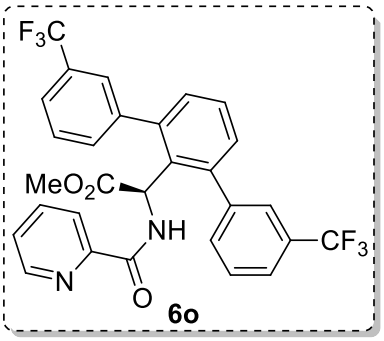
Following the general procedure, **6m** was obtained after purification by column chromatography on silica gel (EtOAc:hexane = 30:70); Rf = 0.7 (EtOAc : Hex = 30:70); as an oily liquid; yield: 52% (60 mg) ; IR (KBr): cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 8.59 (d, 1H, *J* = 0.3 Hz), 8.38 (d, 1H, *J* = 8.1 Hz), 8.05 (d, 1H, *J* = 7.8 Hz), 7.78 (t, 1H, *J* = 7.6 Hz), 7.59 – 7.24 (m, 12H), 6.00 (d, 1H, *J* = 8.2 Hz), 3.72 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 171.1, 162.9, 149.1, 142.8, 141.6, 137.1, 133.3, 132.7, 130.8, 130.4, 129.7, 128.2, 127.6, 126.1, 122.4, 122.1, 53.0, 52.9; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{27}H_{21}Br_2N_2O_3$: 578.9919; found 578.9940.

(*R*)-Methyl 2-(4,4''-bis(trifluoromethyl)-[1,1':3',1''-terphenyl]-2'-yl)-2-(picolinamido)acetate (6n):



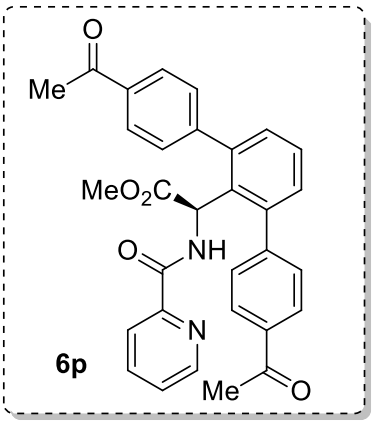
Following the general procedure, **6n** was obtained after purification by column chromatography on silica gel (EtOAc:hexane = 25:75); Rf = 0.8 (EtOAc : Hex = 30:70); as a colorless solid; yield: 40% (45 mg) ; mp 166-168 ^oC ; IR (KBr): 3382, 3066, 2946, 1745, 1681, 1616 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 8.44 (d, 1H, *J* = 4.4 Hz), 8.23 (d, 1H, *J* = 7.7 Hz), 8.02 (d, 1H, *J* = 7.8 Hz), 7.81-7.69 (m, 5H), 7.55 – 7.25 (m, 8H), 5.95 (d, 1H, *J* = 7.8 Hz), 3.70 (s, 3H) ; ^{13}C NMR (100 MHz, $CDCl_3$): δ 171.0, 162.8, 148.8, 148.1, 144.7, 141.7, 137.2, 132.9, 130.5, 130.0 – 129.7 (m), 127.7, 126.4, 125.2 (q, *J* = 3.5 Hz), 121.9, 53.1, 53.0; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{29}H_{21}F_6N_2O_3$: 559.1456 ; found 559.1434.

(R)-methyl 2-(3,3''-bis(trifluoromethyl)-[1,1':3',1''-terphenyl]-2'-yl)-2-(picolinamido)acetate (6o): Following the general procedure, **6o** was obtained after purification by column chromatography on silica gel (EtOAc:hexane = 28:72); Rf = 0.7 (EtOAc : Hex = 30:70); as an oily liquid; yield: 50% (55 mg) ; IR (KBr): 3385, 3066, 2954, 1747, 1682, 1507 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 8.47 (d, 1H, *J* = 2.0 Hz), 8.30 (d, 1H, *J* = 7.3 Hz), 8.02 (d, 1H, *J* = 7.8 Hz),



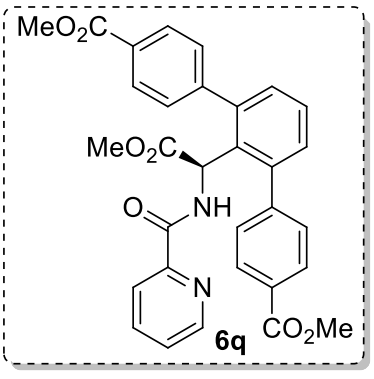
7.77 (t, 1H, *J* = 7.6 Hz), 7.72 – 7.60 (m, 8H), 7.45 (t, 1H, *J* = 7.7 Hz), 7.39 (t, 1H, *J* = 5.6 Hz), 7.29 (d, 2H, *J* = 7.1 Hz), 5.88 (d, 1H, *J* = 7.7 Hz), 3.70 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.9, 162.9, 149.0, 148.2, 141.3-141.7 (m), 141.5, 137.1, 133.3, 133.0 – 132.8 (m), 130.6, 130.3, 128.7, 127.7, 126.5 – 126.4 (m), 126.2, 125.4, 124.6 (q, J_1 = 7.2 Hz, J_2 = 3.6 Hz), 122.7, 122.0, 53.0, 52.8; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{29}H_{20}F_6N_2O_3$: 559.1456; found 559.1442.

(*R*)-Methyl 2-(4,4''-diacetyl-[1,1':3',1''-terphenyl]-2'-yl)-2-(picolinamido)acetate (6p):



Following the general procedure, **6p** was obtained after purification by column chromatography on silica gel (EtOAc:hexane = 80:20); Rf = 0.1 (EtOAc : Hex = 30:70); as a colorless solid; yield: 80% (81 mg) ; mp 166-168 ^oC ; IR (KBr): 3374, 3056, 2953, 1742, 1682, 1507 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.45 (t, 1H, *J* = 4.5 Hz), 8.29 (t, 1H, *J* = 8.0 Hz), 8.05 – 8.00 (m, 5H), 7.77 (t, 1H, *J* = 7.68 Hz), 7.54-7.52 (m, 4H), 7.46 – 7.38 (m, 2H), 7.29 – 7.25 (m, 2H), 5.99 (t, 1H, *J* = 8.0 Hz), 3.68 (s, 3H), 2.68 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 197.8, 171.0, 162.9, 148.9, 148.1, 148.0, 145.9, 142.1, 137.2, 136.3, 132.8, 130.3, 129.9, 128.3, 127.7, 126.3, 122.1, 53.0, 53.0, 26.8; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{31}H_{27}N_2O_5$: 507.1920; found 507.1908.

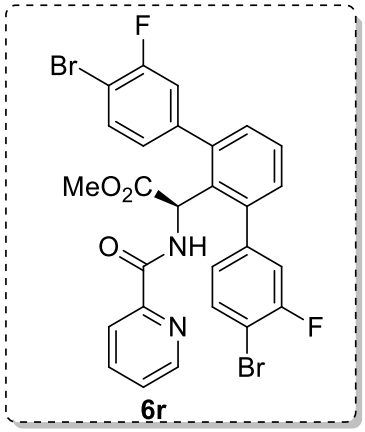
(*R*)-Dimethyl 2'-(2-methoxy-2-oxo-1-(picolinamido)ethyl)-[1,1':3',1''-terphenyl]-4,4''-dicarboxylate (6q): Following the general procedure, **6q** was obtained after purification by



column chromatography on silica gel (EtOAc:hexane =80:20); Rf = 0.1 (EtOAc : Hex = 30:70); as a colorless solid; yield: 64% (68mg) ; mp 190-192 ^oC ; IR (KBr): 3381, 3004, 2952, 1723, 1681, 1508 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.48 – 8.46 (m, 1H), 8.29 (d, 1H, *J* = 8.2 Hz), 8.13 (d, 4H, *J* = 8.3 Hz), 8.03 – 8.00 (m, 1H), 7.78 (td, 1H, J_1 = 7.7 Hz, J_2 = 1.7 Hz), 7.50 (d, 4H, *J* = 8.5 Hz), 7.45 – 7.38 (m, 2H), 7.27 (d, 2H, *J* = 1.7 Hz), 6.00 (d, 1H, *J* = 8.2 Hz), 3.97 (s, 6H), 3.66 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 171.1, 166.9, 162.8, 149.0, 148.1, 145.7, 142.2, 137.1, 132.9, 130.3, 129.7, 129.5, 129.4, 127.6,

126.3, 122.0, 52.9, 52.88, 52.2; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{31}H_{27}N_2O_7$: 539.1818; found 539.1796.

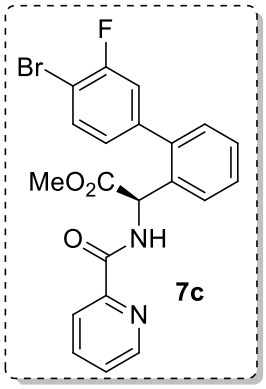
(*R*)-Methyl2-(4,4''-dibromo-3,3''-difluoro-[1,1':3',1''-terphenyl]-2'-yl)-2-(picolinamido)acetate (6r): Following the general procedure, **6r** was obtained after purification



6r

by column chromatography on silica gel (EtOAc:hexane = 28:72); Rf = 0.7 (EtOAc : Hex = 30:70); as a colorless solid; yield: 28% (34mg) ; mp 98-100 ^oC ; IR (KBr): 3381, 3077, 2954, 1744, 1679, 1509 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 8.54 (d, 1H, *J* = 4.0 Hz), 8.34 (d, 1H, *J* = 7.8 Hz), 8.03 (d, 1H, *J* = 7.8 Hz), 7.80 (td, 1H, J_1 = 7.6 Hz, J_2 = 1.4 Hz), 7.64 – 7.61 (m, 2H), 7.44 – 7.39 (m, 2H), 7.28 – 7.18 (m, 4H), 7.09 (d, 2H, *J* = 7.1 Hz), 6.00 (d, 1H, *J* = 8.1 Hz), 3.72 (s, 3H) ; ^{13}C NMR (100 MHz, $CDCl_3$): δ 171.0, 162.8, 159.9, 157.4, 148.8, 148.3, 142.0 (d, *J* = 6.9 Hz), 140.8 (d, *J* = 1.1 Hz), 137.2, 133.3, 133.1, 130.5, 127.8, 126.4, 122.0, 118.0 (d, *J* = 21.9 Hz), 108.7 (d, *J* = 20.6 Hz), 53.1, 52.9 ; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{27}H_{19}Br_2F_2N_2O_3$: 614.9730; found 614.9756.

(*R*)-methyl 2-(4'-bromo-3'-fluoro-[1,1'-biphenyl]-2-yl)-2-(picolinamido)acetate (7c):

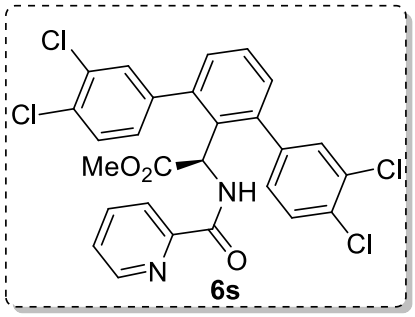


7c

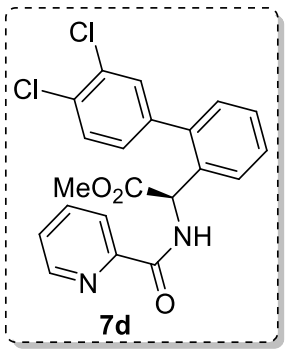
Following the general procedure, **7c** was obtained after purification by column chromatography on silica gel (EtOAc:hexane = 35:65); Rf = 0.6 (EtOAc : Hex = 30:70); as a colorless solid; yield: 48% (42mg) ; IR (KBr): 3383, 3058, 2845, 1744, 1679, 1508 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 8.93 (d, 1H, J = 6.2 Hz), 8.60 (dd, 1H, J_1 = 3.8 Hz, J_2 = 0.5 Hz), 8.12 (dd, 1H, J_1 = 7.8 Hz, J_2 = 0.6 Hz), 7.84 (t, 1H, *J* = 7.7 Hz), 7.65 (t, 1H, *J* = 7.9 Hz), 7.56 (dd, 1H, J_1 = 7.1 Hz, J_2 = 1.8 Hz), 7.47 – 7.25 (m, 7H), 5.80 (d, 1H, *J* = 6.8 Hz), 3.74 (s, 3H) ; ^{13}C NMR (100 MHz, $CDCl_3$): δ 171.1, 163.6, 149.1, 148.3, 141.7 (d, *J* = 7.1 Hz), 140.3 (d, *J* = 1.4 Hz), 137.3, 134.4, 133.4, 130.5, 128.9, 128.6, 127.0, 126.6 (d, *J* = 3.5 Hz), 126.5, 122.3, 118.0 (d, *J* = 22.6 Hz), 108.5, 53.4, 53.0; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{21}H_{17}Br\,FN_2O_3$:443.0407; found 443.0423.

(*R*)-Methyl 2-(picolinamido)-2-(3,3'',4,4''-tetrachloro-[1,1':3',1''-terphenyl]-2'-yl)acetate (6s): Following the general procedure, **6s** was obtained after purification by column chromatography on silica gel (EtOAc:hexane = 28:72); Rf = 0.7 (EtOAc : Hex = 30:70); as a colorless solid; yield: 64% (72mg) ; mp 147-149 ^oC ; IR (KBr): 3382, 3058, 2852, 1744, 1681,

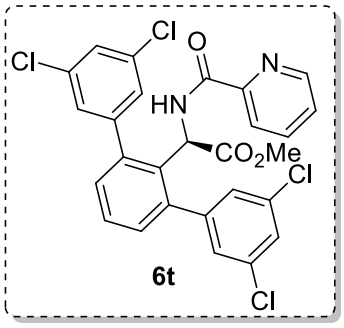
1509 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 8.56 (d, 1H, *J* = 3.8 Hz), 8.36 (d, 1H, *J* = 7.5 Hz), 8.04 (d, 1H, *J* = 7.8 Hz), 7.80 (t, 1H, *J* = 7.6 Hz), 7.52 (s, 4H), 7.44 – 7.23 (m, 5H), 5.96 (d, 1H, *J* = 7.9 Hz), 3.74 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 171.0, 162.9, 148.9, 148.4, 140.7, 137.2, 133.3, 132.4, 132.2, 131.6, 130.6, 130.2, 128.9, 127.8, 126.3, 122.0, 53.1, 53.0 ; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{27}H_{19}Cl_4N_2O_3$: 559.0150; found 559.0126.



(*R*)-Methyl 2-(3',4'-dichloro-[1,1'-biphenyl]-2-yl)-2-(picolinamido)acetate (7d): Following the general procedure, **7d** was obtained after purification by column chromatography on silica gel (EtOAc:hexane = 35:65); Rf = 0.6 (EtOAc : Hex = 30:70); as an oily liquid; yield: 24% (20 mg) ; IR (KBr): 3384, 3054, 2849, 1744, 1679, 1508 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 8.91 (d, 1H, *J* = 6.1 Hz), 8.61 (d, 1H, *J* = 4.3 Hz), 8.12 (d, 1H, *J* = 7.8 Hz), 7.84 (t, 1H, *J* = 7.7 Hz), 7.64 (s, 1H), 7.57 – 7.27 (m, 7H), 5.78 (d, 1H, *J* = 6.7 Hz), 3.74 (s, 3H) ; ^{13}C NMR (100 MHz, $CDCl_3$): δ 171.1, 163.6, 149.1, 148.3, 140.3, 140.1, 137.3, 134.5, 132.4, 131.9, 131.6, 130.6, 130.3, 129.0, 128.9, 128.6, 127.1, 126.5, 122.3, 53.6, 52.9 ; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{27}H_{17}Cl_2N_2O_3$: 415.0616; found 415.0635.

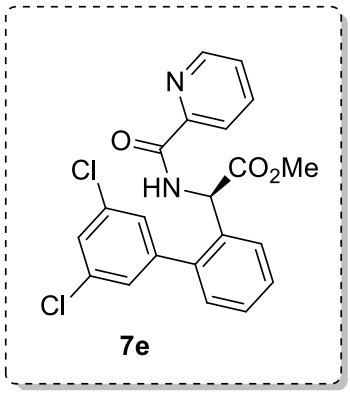


(*R*)-Methyl 2-(picolinamido)-2-(3,3'',5,5''-tetrachloro-[1,1':3',1''-terphenyl]-2'-yl)acetate (6t): Following the general procedure, **6t** was obtained after purification by column chromatography on silica gel (EtOAc:hexane = 20:80); Rf = 0.9 (EtOAc : Hex = 30:70); as a colorless solid; yield: 22% (26 mg) ; mp 148-150 ºC ; IR (KBr): 3375, 3058, 2946, 1743, 1682, 1559 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 8.60 (d, 1H, *J* = 4.7 Hz), 8.39 (d, 1H, *J* = 7.9 Hz), 8.05 (d, 1H, *J* = 7.8 Hz), 7.80 (td, 1H, J_1= 7.7 Hz, J_2= 1.6 Hz), 7.46 – 7.23 (m, 10H), 5.93 (d, 1H, *J* = 8.0 Hz), 3.78 (s, 3H) ; ^{13}C NMR (100 MHz, $CDCl_3$): 171.0, 162.9, 148.9, 148.6, 143.4, 140.5, 137.1, 134.8, 133.4, 130.6, 128.3, 128.2, 128.24, 128.21, 127.8, 126.3, 122.1, 53.2, 52.8; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{27}H_{19}Cl_4N_2O_3$: 559.0150; found 559.0175.



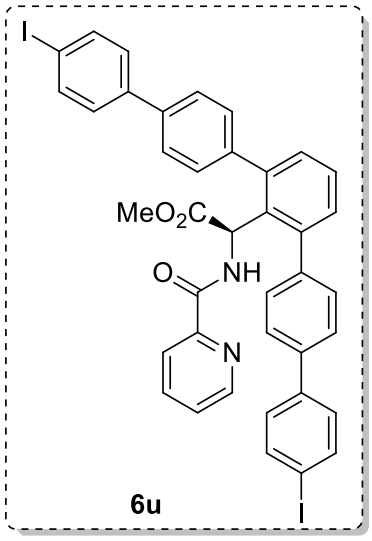
(*R*)-Methyl 2-(3',5'-dichloro-[1,1'-biphenyl]-2-yl)-2-(picolinamido)acetate (7e): Following the general procedure, **7e** was obtained after purification by column chromatography on silica gel

(EtOAc:hexane = 30:70); Rf = 0.7 (EtOAc : Hex = 30:70); as a colorless solid; yield: 52% (43 mg) ; IR (KBr): 3383, 3054, 2954, 1744, 1679, 1558 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 8.88 (d, 1H, *J* = 6.5 Hz), 8.60 (d, 1H, *J* = 4.6 Hz), 8.13 (d, 1H, *J* = 7.8 Hz), 7.84 (t, 1H, *J* = 7.7 Hz), 7.57 (d, 1H, *J* = 7.4 Hz), 7.47 – 7.26 (m, 7H), 5.76 (d, 1H, *J* = 7.0 Hz), 3.75 (s, 3H) ; ^{13}C NMR (100 MHz, $CDCl_3$): 171.0, 163.6, 149.1, 148.3, 143.1, 139.8, 137.3, 134.8, 134.5, 130.5, 129.0, 128.6, 128.2, 127.8, 127.5, 126.5, 122.3, 53.7, 53.0 ; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{21}H_{17}Cl_2N_2O_3$: 415.0616; found 415.0636.



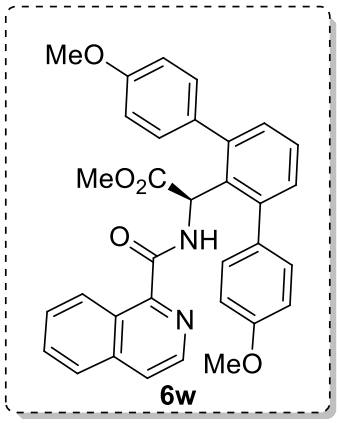
7e

(*R*)-methyl2-(4,4''''-diiodo-[1,1':4',1'':3'',1''':4''',1''''-quinquephenyl]-2''-yl)-2-(picolinamido)acetate (6u): Following the general procedure, **6u** was obtained after purification by column chromatography on silica gel (EtOAc:hexane = 30:70); Rf = 0.7 (EtOAc : Hex = 30:70); as a colorless solid; yield: 28% (46 mg) ; mp 145-147 ^oC ; IR (KBr): 3375, 3055, 2957, 1742, 1680, 1509 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 8.44-8.40 (m, 2H), 8.05 (d, 1H, *J* = 7.8 Hz), 7.83 – 7.75 (m, 6H), 7.65 (d, 4H, *J* = 8.2 Hz), 7.52 (d, 4H, *J* = 8.2 Hz), 7.44 – 7.28 (m, 9H), 6.17 (d, 1H, *J* = 8.4 Hz), 3.68 (s, 3H) ; ^{13}C NMR (100 MHz, $CDCl_3$): δ 171.4, 162.9, 149.3, 148.0, 142.6, 140.6, 140.3, 139.2, 137.9, 137.1, 133.3, 130.4, 130.1, 129.0, 127.6, 126.7, 126.2, 122.1, 93.2, 53.2, 52.8 ; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{39}H_{29}I_2N_2O_3$: 827.0268; found 827.0301.



6u

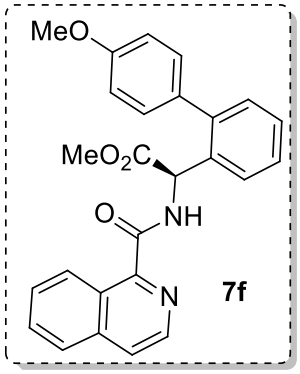
(*R*)-Methyl2-(4,4''-dimethoxy-[1,1':3',1''-terphenyl]-2'-yl)-2-(isoquinoline-1-carboxamido) acetate (6w): Following the general procedure, **6w** was obtained after purification by column chromatography on silica gel (EtOAc:hexane = 60:40); Rf = 0.3 (EtOAc : Hex = 30:70); as a colorless solid; yield: 53% (57 mg) ; mp 177-179 ^oC ; IR (KBr): 3370, 3062, 2838, 1745, 1675, 1512 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 9.47 (d, 1H, *J* = 8.6 Hz), 8.61 (d, 1H, *J* = 8.8 Hz), 8.43 (d, 1H, *J* = 5.5 Hz), 7.82 (d, 1H, *J* = 8.1 Hz), 7.78 (d, 1H, *J* = 5.5 Hz), 7.70-7.67 (m, 1H), 7.64-7.60 (m, 1H), 7.40 – 7.37 (m, 5H), 7.28 – 7.26 (m, 2H),



6w

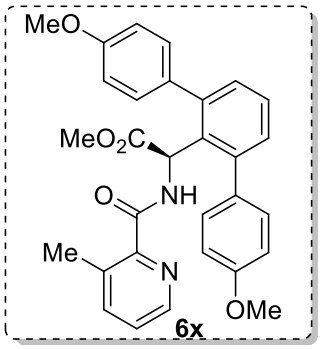
6.99 (d, 4H, *J* = 8.4 Hz), 6.23 (d, 1H, *J* = 8.9 Hz), 3.88 (s, 6H), 3.63 (s, 3H) ; ^{13}C NMR (100 MHz, $CDCl_3$): δ 171.7, 164.4, 159.1, 147.6, 142.8, 140.1, 137.2, 133.9, 133.4, 130.7, 130.4, 130.3, 128.5, 127.8, 127.3, 127.0, 126.7, 124.2, 113.6, 55.3, 52.8, 52.6; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{33}H_{29}N_2O_5$:533.2076; found 533.2107.

(*R*)-Methyl 2-(isoquinoline-1-carboxamido)-2-(4'-methoxy-[1,1'-biphenyl]-2-yl)acetate (7f):



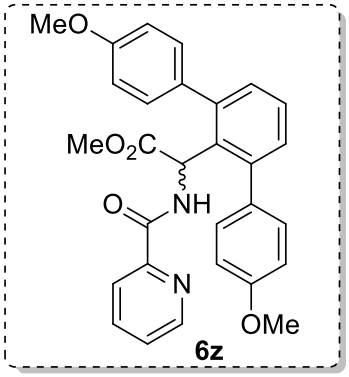
Following the general procedure, **7f** was obtained after purification by column chromatography on silica gel (EtOAc:hexane = 65:35); Rf = 0.4 (EtOAc : Hex = 30:70); as a colorless solid; yield: 28% (24 mg) ; mp 100-102 ^oC ; IR (KBr): 3386, 3062, 2838, 1745, 1674, 1505 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.55 (d, 1H, *J* = 8.5 Hz), 8.98 (d. 1H, *J* = 6.6 Hz), 8.50 (d, 1H, *J* = 5.4 Hz), 7.86 – 7.62 (m, 5H), 7.49 – 7.34 (m, 5H), 7.01 (d, 2H, *J* = 8.2 Hz), 5.93 (d, 1H, *J* = 6.8 Hz), 3.87 (s, 3H), 3.74 (s, 3H) ; ^{13}C NMR (100 MHz, $CDCl_3$): δ 171.7, 165.3, 159.1, 147.3, 142.4, 140.4, 137.3, 134.4, 132.6, 131.1, 130.7, 130.5, 128.7, 128.5, 127.9, 127.8, 127.2, 127.1, 126.8, 124.6, 113.8, 55.3, 53.9, 52.7; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{26}H_{23}N_2O_4$:427.1658; found 427.1680.

(*R*)-Methyl 2-(4,4''-dimethoxy-[1,1':3',1''-terphenyl]-2'-yl)-2-(3-methylpicolinamido)acetate



(6x): Following the general procedure, **6x** was obtained after purification by column chromatography on silica gel (EtOAc:hexane = 65:35); Rf = 0.4 (EtOAc : Hex = 30:70); as a colorless solid; yield: 87% (86 mg) ; mp 158-160 ^oC ; IR (KBr): 3371, 3054, 2932, 1746, 1678, 1512 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.53 (d, 1H, J = 8.8 Hz), 8.35 (d, 1H, *J* = 3.5 Hz), 7.51 (d, 1H, *J* = 7.6 Hz), 7.38-7.36 (m, 5H), 7.27-7.25 (m, 3H), 6.99-6.97 (m, 4H), 6.16 (d, 1H, *J* = 9.0 Hz), 3.87 (s, 6H), 3.60 (s, 3H), 2.64 (s, 3H) ; ^{13}C NMR (100 MHz, $CDCl_3$): δ 171.8, 164.4, 159.1, 146.9, 145.2, 142.8, 140.5, 135.4, 134.0, 133.4, 130.7, 130.4, 127.3, 125.5, 113.6, 55.3, 52.6, 52.5, 20.4 ; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{30}H_{29}N_2O_5$: 497.2076; found 497.2059.

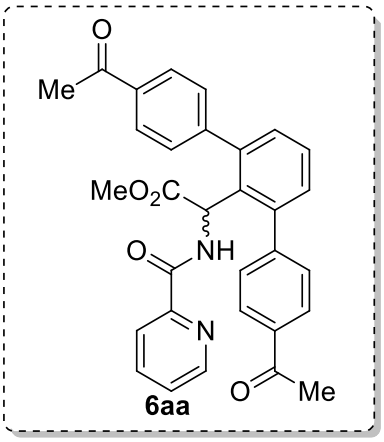
Methyl 2-(4,4''-dimethoxy-[1,1':3',1''-terphenyl]-2'-yl)-2-(picolinamido)acetate (6z): Following the general procedure, **6z** was obtained after purification by column chromatography on silica gel (EtOAc:hexane = 60:40); Rf = 0.4 (EtOAc : Hex = 30:70); as a colorless solid; yield: 72% (70 mg) ; mp 180-182 ^oC ; IR (KBr): 3377, 2961, 2830, 1744, 1680, 1512 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.52 (d, 1H, J = 4.4 Hz), 8.44 (d, 1H, *J* = 8.6 Hz), 8.06 (d, 1H, *J* = 7.8 Hz),



6z

7.77 (t, 1H, *J* = 7.7 Hz), 7.40 – 7.24 (m, 8H), 7.00 (d, 4H, *J* = 8.1 Hz), 6.17 (d, 1H, *J* = 8.7 Hz), 3.89 (s, 6H), 3.65 (s, 3H) ; ^{13}C NMR (100 MHz, $CDCl_3$): δ 171.5, 162.9, 159.1, 149.5, 147.9, 142.7, 137.0, 133.9, 133.4, 130.7, 130.4, 127.4, 126.1, 122.2, 113.6, 55.3, 52.9, 52.6 ; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{29}H_{27}N_2O_5$: 483.1920; found 483.1902.

Methyl 2-(4,4''-diacetyl-[1,1':3',1''-terphenyl]-2'-yl)-2-(picolinamido)acetate (6aa):



6aa

Following the general procedure, **6aa** was obtained after purification by column chromatography on silica gel (EtOAc:hexane = 80:20); Rf = 0.1 (EtOAc : Hex = 30:70); as a colorless solid; yield: 80% (81 mg) ; mp 187-189 ^oC ; IR (KBr): 3377, 3056, 2957, 1743, 1682, 1508 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.44 (d, 1H, *J* = 4.5 Hz), 8.29 (d, 1H, *J* = 7.9 Hz), 8.05 – 8.00 (m, 5H), 7.77 (t, 1H, *J* = 7.7 Hz), 7.52 (d, 4H, *J* = 7.8 Hz), 7.45 – 7.38 (m, 2H), 7.26 (d, 2H, *J* = 7.6 Hz), 5.99 (d, 1H, *J* = 8.0 Hz), 3.67 (s, 3H), 2.67 (s, 6H) ; ^{13}C NMR (100 MHz, $CDCl_3$): δ 197.8, 171.0, 162.9, 149.0, 148.1, 145.9, 142.1, 137.2, 136.3, 132.8, 130.3, 129.9, 128.3, 127.7, 126.3, 122.1, 53.0, 52.9, 26.8 ; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{31}H_{27}N_2O_5$: 507.1920; found 507.1909.

References

1) a) Dupont, J.; Consorti, C. S.; Spencer, J. *Chem. Rev.* **2005**, *105*, 2527. b) Lyons, T. W.; Sanford, M. S.; *Chem. Rev.* **2010**, *110*, 1147. c) Rouquet, G.; Chatani, N. *Angew. Chem. Int. Ed.* **2013**, *52*, 11726. d) Liu, J.; Chen, G.; Tan, Z. *Adv. Synth. Catal.* **2016**, *358*, 1174.

2) a) Yang, Y.; Wang, X.; Li, Y.; Zhou, B. *Angew. Chem. Int. Ed.* **2015**, *54*, 15400. b) Le, J.; Gao, Y.; Ding, Y.; Jiang, C. *Tetrahedron Lett.*, **2016**, *57*, 1728. c) Mishra, A.; Vats, T. K.; Deb, I. *J. Org. Chem.* **2016**, *81*, 6525. d) Dangel, B. D.; Godula, K.; Youn, S. W.; Sezen, B.; Sames, D. *J. Am. Chem. Soc.* **2002**, *124*, 11856. e) Ahrendt, K. A.; Bergman, R. G.; Ellman, J. A. *Org. Lett.* **2003**, *5*, 1301. f) Bowie, A. L. Jr.; Hughes, C. C.; Trauner, D. *Org. Lett.* **2005**, *7*, 5207. g) Leblanc, M.; Fagnou, K. *Org. Lett.* **2005**, *7*, 2849. h) O'Malley, S. J.; Tan, K. L.; Watzke, A.; Bergman, R. G.; Ellman, J. A. *J. Am. Chem. Soc.* **2005**, *127*, 13496. i) Larivée, A.; Mousseau, J. J.; Charette,

A. B. *J. Am. Chem. Soc.* **2008**, *130*, 52. j) Chaumontet, M.; Piccardi, R.; Baudoin, O. *Angew. Chem.* **2009**, *121*, 185; *Angew. Chem. Int. Ed.* **2009**, *48*, 179. k) Wang, D. -H.; Yu, J. -Q. *J. Am. Chem. Soc.* **2011**, *133*, 5767. l) Gutekunst, W. R.; Baran, P. S. *J. Am. Chem. Soc.* **2011**, *133*, 19076.

3) a) Young, T. S.; Schultz, P. G. *J. Biol. Chem.* **2010**, *285*, 11039. b) Kast, P. ChemBioChem, **2011**, *12*, 2395. c) Sommer, S.; Weikart, N. D.; Brockmeyer, A.; Janning, P.; Mootz, H. D. *Angew. Chem. Int. Ed.* **2011**, *50*, 9888. d) Stevenazzi, A.; Marchini, M.; Sandrone, G.; Vergani, G.; Lattanzio, M. *Bioorg. Med. Chem. Lett.* **2014**, *24*, 5349.

4) a) Al Toma, R. S.; Brieke, C.; Cryle, M. J.; Süssmuth, R. D. *Nat. Prod. Rep.,* **2015**, *32*, 1207. b) Nam, J.; Shin, D.; Rew, Y.; Boger, D. L. *J. Am. Chem. Soc.,* **2007**, *129*, 8747. c) Nicolaou, K. C.; Boddy, C. N.; Brase, S.; Winssinger, N. *Angew. Chem., Int. Ed. Engl.*, **1999**, *38*, 2096.

5) a) Vanderhaeghe, H.; Janssen, G.; Compernolle, F. *Tetrahedron Lett.,* **1971**, *12*, 2687. b) Cocito, C. *Microbiol. Rev.,* **1979**, *43*, 145. c) Mast, Y.; Wohlleben, W. *Int. J. Med. Microbiol.,* **2014**, *304*, 44. d) Crooy, P.; De Neys, R. *J. Antibiot.,* **1972**, *25*, 371. e) Hänchen, A.; Rausch, S.; Landmann, B.; Toti, L.; Nusser, A.; Süssmuth, R. D. *ChemBioChem.,* **2013**, *14*, 625. f) Teshima, T.; Nishikawa, M.; Kubota, I.; Shiba, T.; Iwai, Y.; Omura, S. *Tetrahedron Lett.,* **1988**, *29*, 1963. g) Aoki, H.; Ōkuhara, M. *Ann. Rev. Microbial.,* **1980.** *34*, 159. h) Chen, K. X.; Njoroge, F. G.; Pichardo, J.; Prongay, A.; Butkiewicz, N.; Yao, N.; Madison, V.; Girijavallabhan V. *J. Med. Chem.,* **2006**, *49*, 567. i) Nishino, N.; Hayashida, J.; Arai, T.; Mihara, H.; Ueno, Y.; Kumagai, H. *J. Chem. Soc., Perkin Trans. 1,* **1996**, 939. j) Sheehan, S. M.; Masters, J. J.; Wiley, M. R.; Young, S. C.; Liebeschuetz, J. W.; Jones, S. D.; Murray, C. W.; Franciskovich, J. B.; Engel, D. B.; Weber, W. W.; Marimuthu, J.; Kyle, J. A.; Smallwood, J. K.; Farmen, M. W.; Smith, G. F. *Bioorg. Med. Chem. Lett.*, **2003**, *13*, 2255. k) Wang, C. -L.; Fan, Y. -B.; Lu, H. -H.; Tsai, T. -H.; Tsai, M. -C.; Wang, H. -P. *J. Biomed. Sci.,* **2010**, *17*, 71. l) Oost, T. K.; Sun, C.; Armstrong, R. C.; Al-Assaad, A.; Betz, S. F.; Deckweth, T. L.; Ding, H.; Elmore, S. W.; Meadows, R. P.; Olejniczak, E. T.; Olesksijew, A.; Oltersdorf, T.; Rosenberg, S. H.; Shoemaker, A. R.; Tomaselli, K. J.; Zou, H.; Fesik, S. W. *J. Med. Chem.*, **2004**, *47*, 4417.

6) a) Hashimoto, M.; Komori, T.; Kamiya, T. *J. Antibiot.,* **1976**, *29*, 890. b) Gaudelli, N. M.; Townsend, C. A. *Nat. Chem. Biol.,* **2014**, *10*, 251. c) Chan, J. A.; Shultis, E. A.; Dingerdissen, J. J.; Debrosse, C. W.; Roberts, G. D.; Snade, K. M. *J. Antibiot.,* **1985**, *38*, 139. d) Hida, T.; Tsubotani, S.; Katayama, N.; Okazaki, H.; Harada, S. *J. Antibiot.,* **1985**, *38*, 1128. e) Vértesy, L.; Aretz, W.; Knauf, M.; Markus, A.; Vogel, M.; Wink, J. *J. Antibiot.,* **1999**, *52*, 374.

7) a) Seayad, A. M.; Ramalingam, B.; Yoshinaga, K.; Nagata, T.; Chai, C. L. L. *Org. Lett.*, **2010**, *12*, 264. b) Okrasa, K.; Levy, C.; Wilding, M.; Goodall, M.; Baudendistel, N.; Hauer, B.; Leys, D.; Micklefield, J. *Angew. Chem. Int. Ed.* **2009**, *48*, 7691. c) Ntaganda, R.; Milovic, T.; Tiburcioz, J.; Thadani, A. N. *Chem. Commun.,* **2008**, 4052. d) Micskei, K.; Holczknecht, O.; Hajdu, C.; Patonay, T.; Marchis, V.; Meo, M.; Zucchi, C.; Pályi, G. J. Organomet. Chem., **2003**, *682*, 143. e) Langen, L. M.; Oosthoek, N. H. P.; Rantwijk, F.; Sheldon, R. A. *Adv. Synth. Catal.* **2003**, *345*, 797. f) Demir, A. S.; Sesenoglu, Ö. *Helv. Chim. Acta*., **2003**, *86*, 91. f) Kitamura, M.; Lee, D.; Hayashi, S.; Tanaka, S.; Yoshimura, M. *J. Org. Chem.* **2002**, *67*, 8685. g) Wang, M. -X.; Lin, S. -J. *J. Org. Chem.* **2002**, *67*, 6542.

8) a) Gröger, H. *Chem. Rev.* **2003,** *103*, 2795.

9) a) Williams, T. J.; Reay, A. J.; Whitwood, A. C.; Fairlamb, J. S. *Chem. Commun.*, **2014**, *50*, 3052. b) Meyer, F. -M.; Liras, S.; Guzman-Perez, A.; Perreault, C.; Bian, J.; James, K. *Org. Lett.*, **2010**, *12*, 3870. c) Deprez, N. R.; Kalyani, D.; Krause, A.; Sanford, M. S. *J. Am. Chem. Soc.*, **2006**, *128*, 4972. d) Yuan, K.; Doucet, H. *Chem. Sci.*, **2014**, *5*, 392.

10) a) Bedford, R. B.; Haddow, M. F.; Webster, R. L.; Mitchell, C. J. *Org. Biomol. Chem.* **2009**, *7*, 3119. b) Ruiz-Rodríguez, J.; Albericio, F.; Lavilla, R. *Chem. Eur. J.* **2010**, *16*, 1124. c) Preciado, S.; Mendive-Tapia, L.; Albericio, F.; Lavilla, R. *J. Org. Chem.* **2013**, *78*, 8129. d) Mahindra, A.; Bagra, N.; Jain, R. *J. Org. Chem.* **2013**, *78*, 10954. e) Williams, T. J.; Reay, A. J.; Whitwood, A. C.; Fairlamb, I. J. S. *Chem. Commun.* **2014**, *50*, 3052. f) Kallepalli, V. A.; Shi, F.; Paul, S.; Onyeozili, E. N.; Maleczka, R. E.; Smith, M. R. *J. Org. Chem.* **2009**, *74*, 9199. g) Meyer, F.-M.; Liras, S.; Guzman-Perez, A.; Perreault, C.; Bian, J.; James, K. *Org. Lett.* **2010**, *12*, 3870. h) Vickers, C. J.; Mei, T.-S.; Yu, J.-Q. *Org. Lett.* **2010**, *12*, 2511. i) Li, J.-J.; Mei, T.-S.; Yu, J.-Q. *Angew. Chem., Int. Ed.* **2008**, *47*, 6452.

11) a) Zaitsev, V. G.; Shabashov, D.; Daugulis, O. *J. Am. Chem. Soc.* **2005**, *127*, 13154. b) Gou, F. -R.; Wang, X. -C.; Huo, P. -F.; Bi, H. -P.; Guan, Z. -H.; Liang, Y. -M. *Org. Lett.*, **2009**, *11*, 5726. c) Cheng, T.; Yin, W.; Zhang, Y.; Zhang, Y.; Huang, Y. *Org. Biomol. Chem.*, **2014**, *12*, 1405. d) Zhao, Y.; Chen, G. *Org. Lett.*, **2011**, *13*, 4850. e) Nack, W. A.; Wang, X.; Wang, B.; He, G.; Chen, G. *Beilstein J. Org. Chem.* **2016**, *12*, 1243. f) Parella, R.; Babu, S. A. *J. Org. Chem.* **2017**, *82*, 6550.

12) a) Vickers, C. J.; Mei, T. -S.; Yu, J. -Q. *Org. Lett.*, **2010**, *12*, 2511. b) Mei, T. -S.; Leow, D.; Xiao, H.; Laforteza, B. N.; Yu, J. -Q. *Org. Lett.*, **2013**, *15*, 3058. c) Zhang, S. -Y.; He, G.; Nack,

W. A.; Zhao, Y.; Li, Q.; Chen, G. *J. Am. Chem. Soc.* **2013**, *135*, 2124. d) Wang, X.; Niu, S.; Xu, L.; Zhang, C.; Meng, L.; Zhang, X.; Ma, D. *Org. Lett.* **2017**, *19*, 246. e) García-Rubia, A.; Laga, E.; Cativiela, C.; Urriolabeitia, E. P.; Gómez-Arrayás, R.; Carretero, J. C. *J. Org. Chem.* **2015**, *80*, 3321. f) Ding, Q.; Ye, S.; Cheng, G.; Wang, P.; Farmer, M. E.; Yu, J. -Q. *J. Am. Chem. Soc.* **2017**, *139*, 417.

13) a) Zhang, L. S.; Chen, G.; Wang, X.; Guo, X. Y.; Zhang, X. S.; Pan, F.; Chen, K.; Shi, Z. J. *Angew. Chem. Int. Ed.* **2014**, *53*, 3899. b) Dastbaravardeh, N.; Toba, T.; Farmer, M. E.; Yu, J. -Q. *J. Am. Chem. Soc.* **2015**, *137*, 9877. c) Xiao, K. -J.; Chu, L.; Yu, J. -Q. *Angew. Chem. Int. Ed.* **2016**, *55*, 2856. d) Zeng, W.; Nukeyeva, M.; Wang, Q.; Jiang, C. *Org. Biomol. Chem.*, **2018**, *16*, 598. e) Jiang, C.; Zeng, W., Synthetic Method of Phenylglycine Derivatives, CN 106279014, Jan 4, 2017. f) Ruiz, S.; Sayago, F. J.; Cativiela, C.; Urriolabeitia, E. P. *J. Mol. Catal. A: Chem.* **2017**, *426*, 407.

Chapter 4: Palladium-catalyzed bidentate ligand directed β-C(sp^3)-H functionalization on ε-, ζ-, η-keto acids.

Introduction

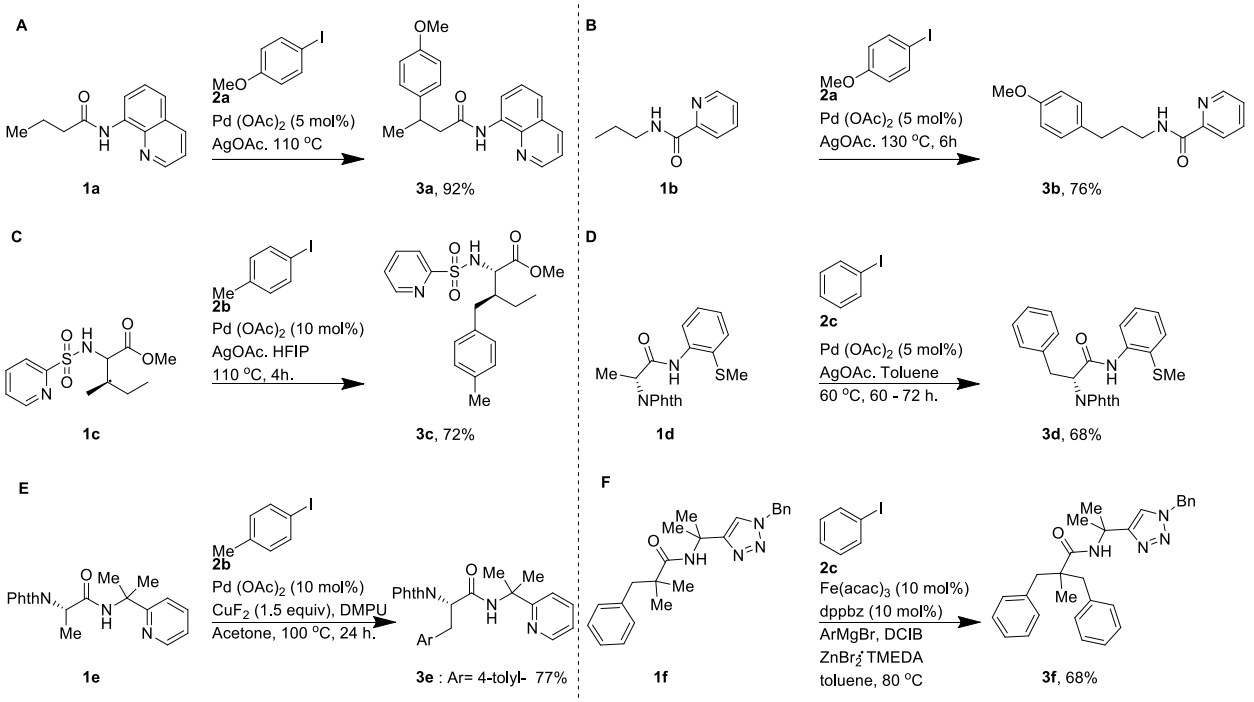
Transition metal-catalyzed mono or bidentate ligand-directed C-H activation and functionalization of C(sp^3)-H and C(sp^2)-H organic molecules is one of the potential tools in organic synthesis, which enables the synthesis of natural products, biologically active molecules and pharmaceutical ingredients.[1,2] In general, due to the relative inertness of C(sp^3)-H bonds, the functionalization of C(sp^3)-H bond is more challenging than the C(sp^2)-H bonds. Given that organic molecules have diverse C-H bonds achieving selective reactivity of desired C-H bond is a challenging task. Early examples of metal-catalyzed C-H functionalization were reported in the late 1930s. Kharasch and Isbell disclosed that arenes are aurated by gold(III) chloride, demonstrating that transition metal complexes can participate in C-H activation chemistry. The report also described arene chlorination is catalyzed by $AuCl_3$, this may be the first example of transition-metal catalysis in C-H bond functionalization.[3a] In 1955, Murahashi[3b] reported cobalt-catalyzed carbonylation to the *ortho*-C(sp^2)-H bond of aromatic aldimine, which afforded isoindolinone. Subsequently, Murahashi reported azo benzene also underwent *ortho*-carbonylation reactions.[3c] Kleiman[3d] and Cope[3e] research groups independently reported cyclometallation pathways for C-H activation.

Currently, this mechanistic approach has been corroborated as C-H activation/functionalization reactions.[3f,2a] In 1967, Fujiwara and Moritani disclosed C-H alkenylation of benzene with styrene palladium chloride complex.[3g] In 1969, the first transition-metal catalyzed C(sp^3)-H functionalization was disclosed by Shilov and co-workers, this report described the reaction of alkanes with Pt salts, which afforded a mixture of alcohols and alkyl halides.[3h-i] Bergman[3j] and Graham[3k] independently reported the oxidative addition of unactivated alkane C-H bonds to iridium metal complex [Cp*(PMe_3) Ir] to form stable alkyl hydride products. In 1993, Murai and co-workers developed an efficient route for directed C(sp^2)-H functionalization on aromatic ketones.[3l] Later, many research groups reported various catalytic directing group-aided C-H functionalization[2j] using different mono or bidentate-directing groups and metal catalysts.[4a-d,2a-c]

To date, the directed C(sp^2)-H bond functionalization can now be considered a reliable tool to access a variety of functional groups. However, functionalization of unactivated C(sp^3)-H bonds remains is still emerging and considered as a challenging process. Along with this line, a part of this thesis envisaged to investigate the Pd-catalyzed bidentate ligand-directed site-selective

functionalization of C(sp^3)-H bonds of keto acids. Some of the literature reports pertaining to the transition metal-catalyzed bidentate ligand-directed site-selective functionalization of C(sp^3)-H bonds have been shown here.

The ability of palladium metal to activate C-H bond via chelation is known since 1960. Nitrogen containing ligands were identified to promote the palladium insertion into the *ortho*-C-H bonds[3e] and later, various C(sp^3)-H bonds.[3m-n] In 2005, Daugulis and Shabashov[5a-d] described the Pd-catalyzed bidentate directing group-directed C-H activation/arylation of β-C(sp^3)-H and β-C(sp^2)-H bonds of carboxamides. These reports introduced 8-aminoquinoline (AQ) and 2-picolinamide bidentate ligands for the site-selective functionalization at β-C(sp^3)-H (Scheme 1A) and γ-C(sp^3)-H, γ-C(sp^2)-H (Scheme 1B) bonds of carboxamides respectively. Later diverse functional group transformations have been reported using these bidentate ligands.[2i]

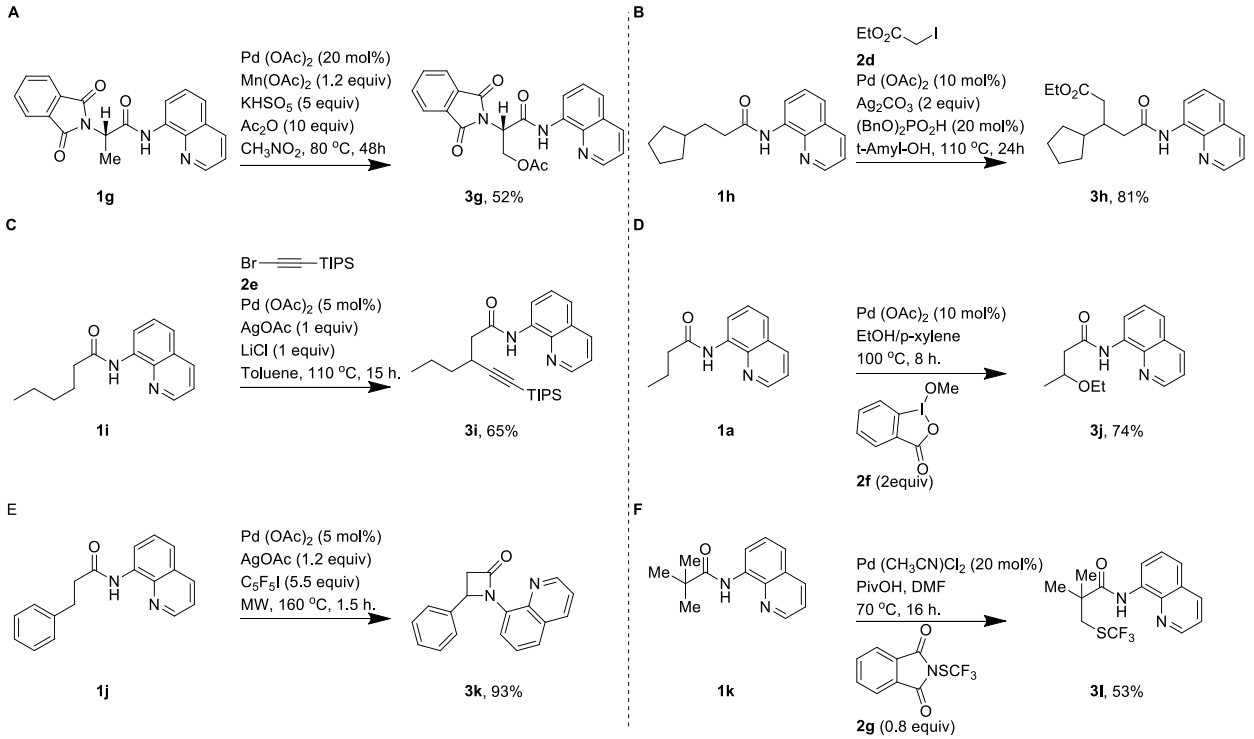


Scheme 1. Pd-catalyzed bidentate directing group-directed site-selective arylation of C(sp^3)-H bonds of carboxamides.

In 2013, Carretero and co-workers described *N*-(2-pyridyl) sulfonyl auxiliary for γ-C-H arylation of amino acid methyl ester **1c**, which successfully afforded γ-arylated compounds **3c** (Scheme 1C).[5e-h] In 2010, Daugulis and Shabashov reported selective mono arylation of primary β-C(sp^3)-H bonds by introducing 2-methylthio aniline as bidentate auxiliary (Scheme 1D)[5c-d]. Shi and co-workers introduced 2-(pyridin-2-yl)isopropyl (PIP) amine as the directing group for the C(sp^3)-H

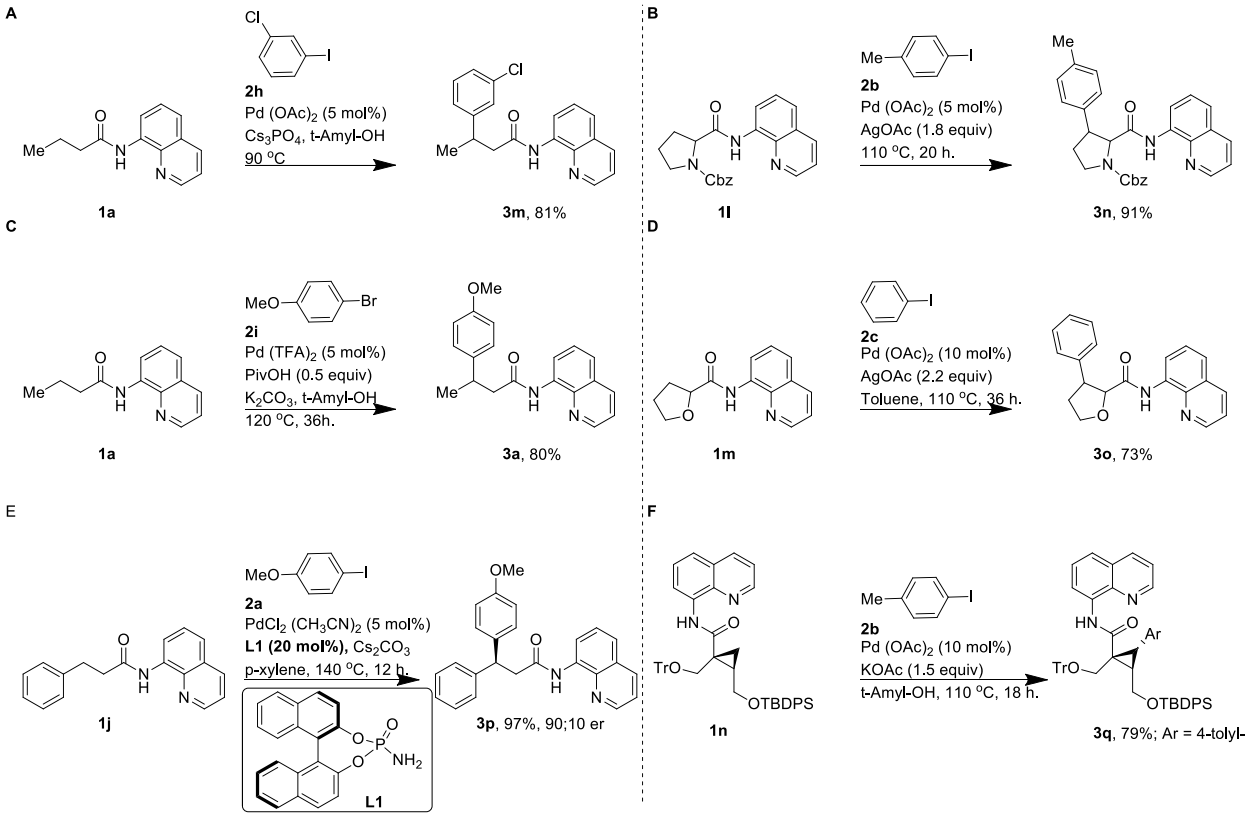
alkoxylation.[5i] Further, PIP-directed mono-arylation of alanine derived amide **1e** with aryl iodide **2b** was reported (Scheme 1E).[5j] In 2014, Ackermann and co-workers introduced triazolyldimethylmethyl (TAM) amine as the directing group for C(sp^3)-H and C(sp^2)-H functionalization (Scheme 1F).[5k] In 2013, Ma and Fan introduced 2-methoxyiminoacetyl (MIA) as the bidentate directing group for the C(sp^3)-H functionalization.[5l]

In 2006, Corey and co-workers reported the Pd-catalyzed bidentate directing group-directed site-selective β-C-H acetoxylation as well as β-C-H arylation of amino acids derivatives (Scheme 2A).[6a] The Pd-catalyzed bidentate directing group-directed β-C(sp^3)-H alkylation of aliphatic carboxamide and amino acids derived amides were also reported (Scheme 2B).[6b] In 2011, Chatani and co-workers disclosed 8-aminoquinoline-directed β-alkynylation of C(sp^3)-H bonds[6c] (Scheme 2C). Rao and co-workers reported an efficient route for the β-C-H alkoxylation of primary and secondary carboxamide (Scheme 2D).[6d] In 2014, Wu and co-workers described intramolecular amination of various carboxamide, which afforded various β-lactams (Scheme 2E).[6e] In 2015, Besset and co-workers disclosed 8-aminoquinoline-directed β-trifluoromethylthiolation of various carboxamides (Scheme 2F).[6f]



Scheme 2. Pd-catalyzed 8-aminoquinoline-directed site-selective functionalization of C(sp^3)-H bonds of carboxamides.

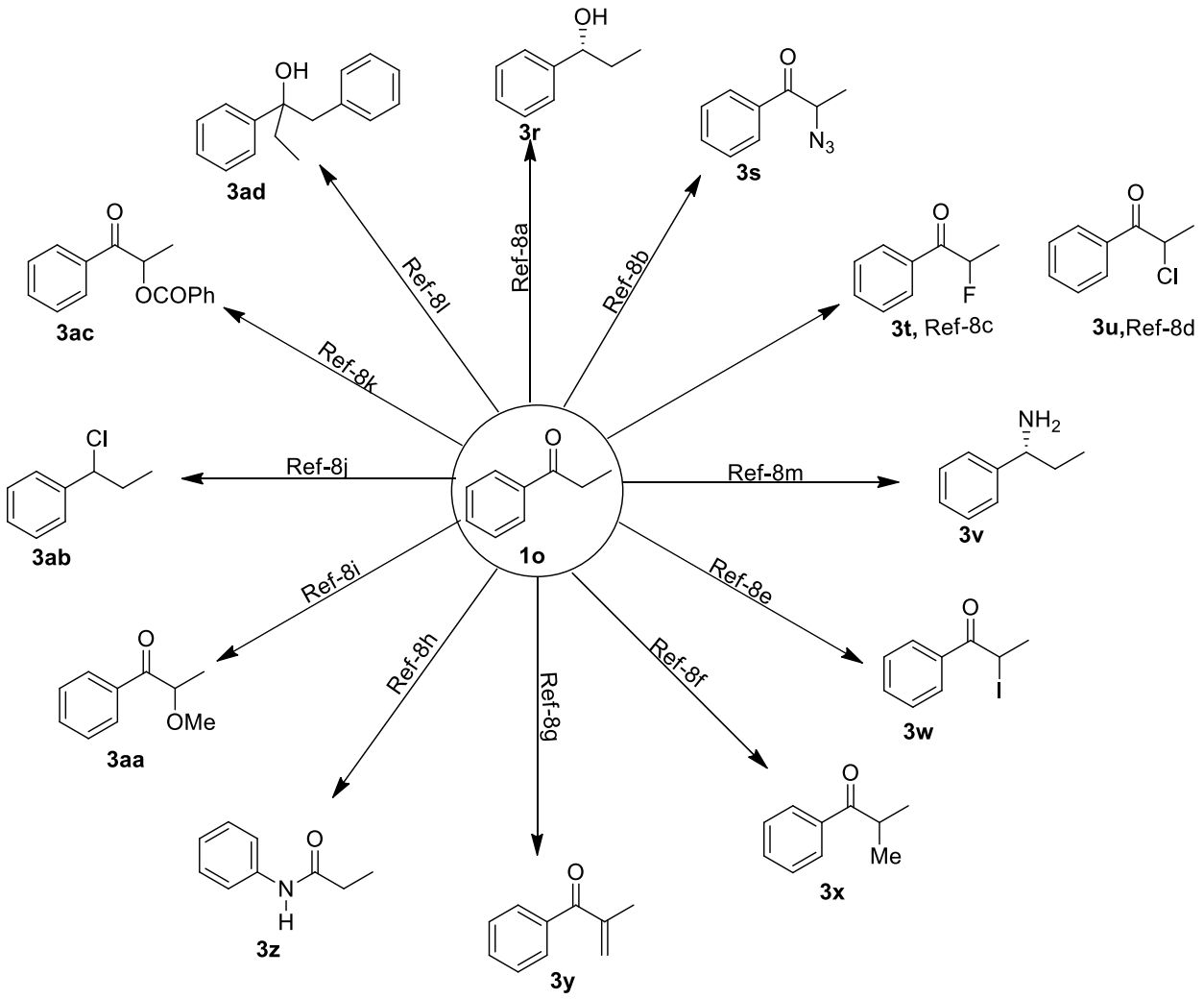
The reaction conditions of the first report on the Pd-catalyzed 8-aminoquinoline-directed C(sp^3)-H arylation of carboxamides (Scheme 1A)[5b] utilizes AgOAc as the iodide scavenger, later, the process was improved by using K_2CO_3 or CsOAc instead of AgOAc (Scheme 3A).[7a] In 2014, Bull and co-workers reported the Pd-catalyzed 8-aminoquinoline-directed C-3 arylation of prolines (Scheme 3B).[7b] Zeng and co-workers disclosed the C(sp^3)-H arylation using aryl bromides as coupling partner (Scheme 3C).[7c] In 2015, our lab reported the regio and stereoselective C-3 arylation of tetrahydrofuran and benzodioxane via the Pd-catalyzed 8-aminoquinoline-directed C(sp^3)-H functionalization strategy (Scheme 3D).[7d-h] Duan and co-workers reported enantioselective arylation of β-C(sp^3)-H bond using chiral phosphoramide ligand **L1** (Scheme 3E).[7i] Shuto and co-workers reported the C(sp^3)-H arylation of tetrasubstituted cyclopropanes (Scheme 3F).[7j,k] There are other significant reports which described the β-C(sp^3)-H arylation via the Pd-catalyzed 8-aminoquinoline-directed C-H functionalization strategy.[7l-o]



Scheme 3. Pd-catalyzed 8-aminoquinoline -directed site-selective arylation of C(sp^3)-H bonds of carboxamides.

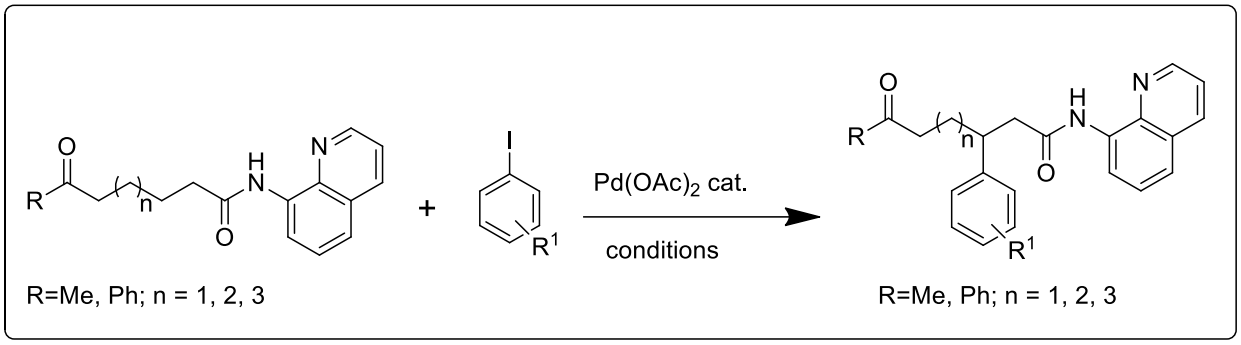
Keto acids are important class of organic molecules in organic synthesis and they serve as synthetic building block for various transformations, which provide access to diverse functionalized organic

molecules through the functionalization of ketone moiety (Scheme 4).[8] In particular, conventional and enzymatic direct reductive amination of keto acids provides amino acids, biologically active



Scheme 4. Functional group transformations of ketone moiety.

molecules, drug candidates as well as ligand[9a-d] and enantioenriched amino acids.[10] Similar to the α-, β-, γ-, δ- amino acid classification, the keto acids can be classified as α-, β-, γ-, δ- keto acids. Accordingly, the direct reductive amination keto acids will provide the valuable non-proteinogenic α-, β-, γ-, δ- natural/unnatural amino acids. Given the importance of α-, β-, γ-, δ- keto acids, a part of this thesis work envisioned to synthesize β-C-H arylated keto acids via the C(sp^3)-H activation methodology. Accordingly, this chapter reports the Pd(II)-catalyzed bidentate directing group, 8-aminoquinoline-directed β-C(sp^3)-H arylation of ε-, ζ-, η-keto acids and the synthesis of corresponding β-C-H functionalized/arylated ε-, ζ-, η-keto acids (Scheme 5).

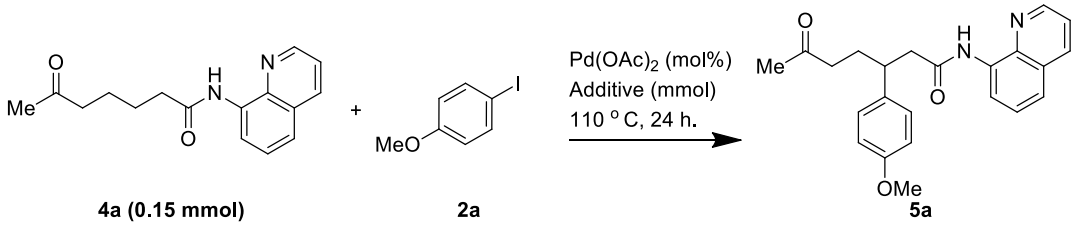


Scheme 5. Pd(II)-catalyzed 8-aminoquinoline-directed β-C(sp^3)-H arylation of ε-, ζ-, η-keto acids.

Results and Discussion

To start with the Pd(II)-catalyzed bidentate directing group, 8-aminoquinoline-directed β-C(sp^3)-H arylation of keto acids, initially ε-keto carboxamide **4a** was assembled from the corresponding keto acid and 8-aminoquinoline. Given that the reaction conditions involving 8-aminoquinoline-directed β-C(sp^3)-H arylation of carboxamide are established well using the $Pd(OAc)_2$ catalyst and AgOAc additive,[5-7] only some required optimization reactions were performed as shown in Table 1. It was also envisaged to perform the Pd(II)-catalyzed bidentate directing group, 8-aminoquinoline-directed β-C(sp^3)-H arylation of keto carboxamides in neat condition without any solvent. Heating a mixture of ε-keto carboxamide **4a** (0.15 mmol) and **2a** (0.3 mmol) in the absence

Table 1. Optimization of Pd(II)-catalyzed 8-aminoquinoline-directed β-C(sp^3)-H arylation of ε-keto carboxamide **4a** with **2a**.



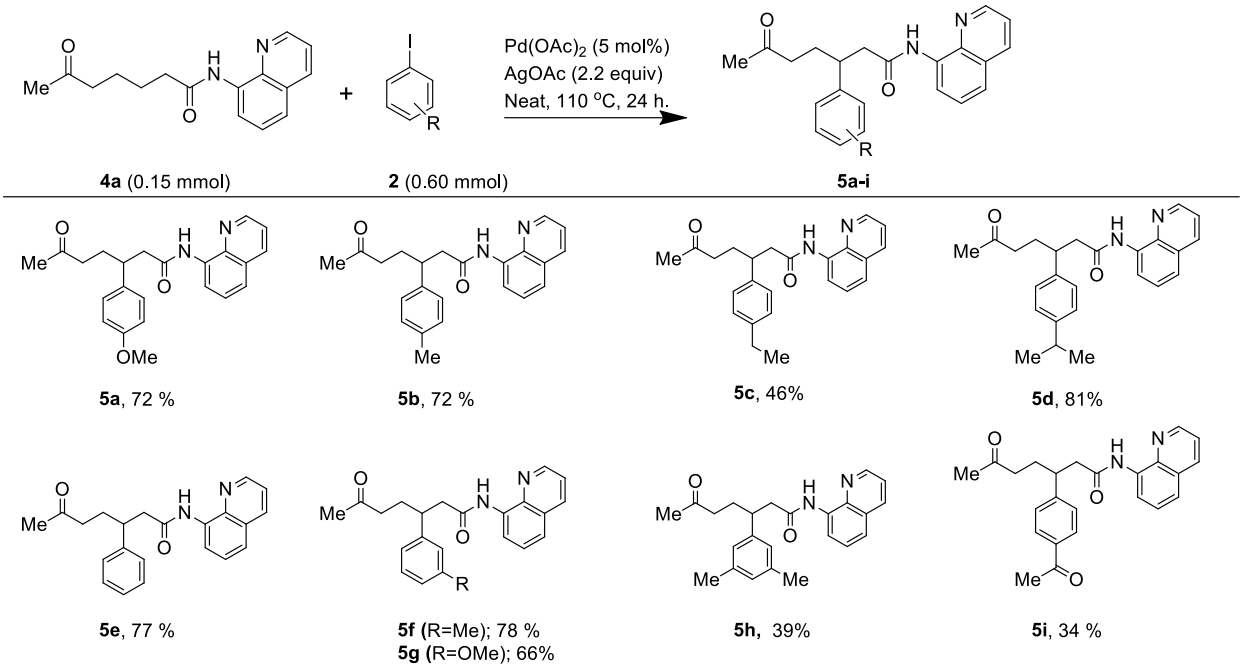
4a (0.15 mmol) **2a** **5a**

Entry	Catalyst (mol%)	**2a** (mmol)	Additive (0.33 mmol)	**5a**;Yield (%)
1	-	0.30	AgOAc	0
2	$Pd(OAc)_2$ (5)	0.30	AgOAc	40
3	$Pd(OAc)_2$ (5)	0.45	AgOAc	57
4	$Pd(OAc)_2$ (5)	0.60	AgOAc	72
5	$Pd(OAc)_2$ (10)	0.60	AgOAc	72

of $Pd(OAc)_2$ catalyst and AgOAc additive at 110 °C, the expected β-C-H arylated product **5a** (Table 1, entry 1) was not obtained. Heating a mixture of carboxamide **4a** (0.15 mmol) and **2a** (0.3

mmol) in the presence of 5 mol% of $Pd(OAc)_2$ catalyst and AgOAc additive at 110 ^oC afforded the product **5a** in 40% yield (Table 1, entry 2). Then, the reaction of carboxamide **4a** (0.15 mmol) and **2a** (0.45 or 0.6 mmol) in the presence of 5 mol% of $Pd(OAc)_2$ catalyst and AgOAc additive at 110 ^oC afforded product **5a** in 57-72% yields (Table 1, entries 3 and 4). Then, the reaction of carboxamide **4a** (0.15 mmol) and **2a** (0.45 or 0.6 mmol) in the presence of 5-10 mol% of $Pd(OAc)_2$ catalyst and AgOAc additive at 110 ^oC afforded product **5a** in 57-72% yields (Table 1, entries 3-5).

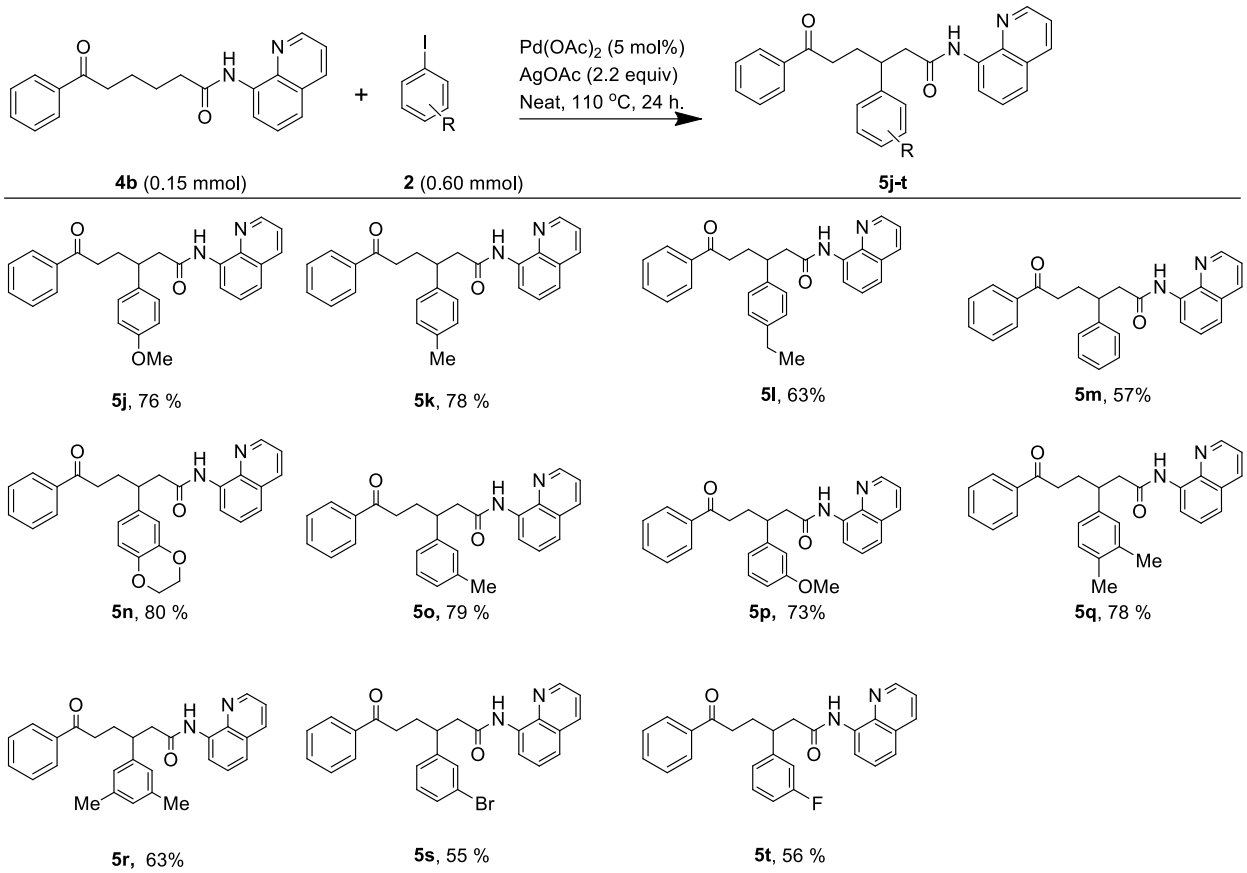
Table 2. Pd(II)-catalyzed 8-aminoquinoline-directed β-C(sp^3)-H arylation of ε-keto carboxamide **4a** with different aryl iodides.



Subsequently, it was envisaged to show the generality and perform the Pd(II)-catalyzed bidentate directing group, 8-aminoquinoline-directed β-C(sp^3)-H arylation of ε-keto carboxamide using different aryl iodides. Accordingly, ε-keto carboxamide **4a** (0.15 mmol) was treated with aryl iodides containing electron-donating substituents e.g., OMe, Me, Et, *i*-Pr at the *para* position and PhI in the presence of 5 mol% of $Pd(OAc)_2$ catalyst and AgOAc additive at 110 ^oC in neat condition. These reactions afforded the corresponding β-C-H arylated products **5a-e** in 46-81% yields (Table 2). Next, the reaction of ε-keto carboxamide **4a** with aryl iodides containing electron-donating substituents e.g., OMe and Me at the *meta* position and electron-withdrawing substituents e.g., Ac in the presence of 5 mol% of $Pd(OAc)_2$ catalyst and AgOAc additive at 110 ^oC in neat

condition also afforded the corresponding β-C-H arylated products **5f-i** in 34-78% yields (Table 2).

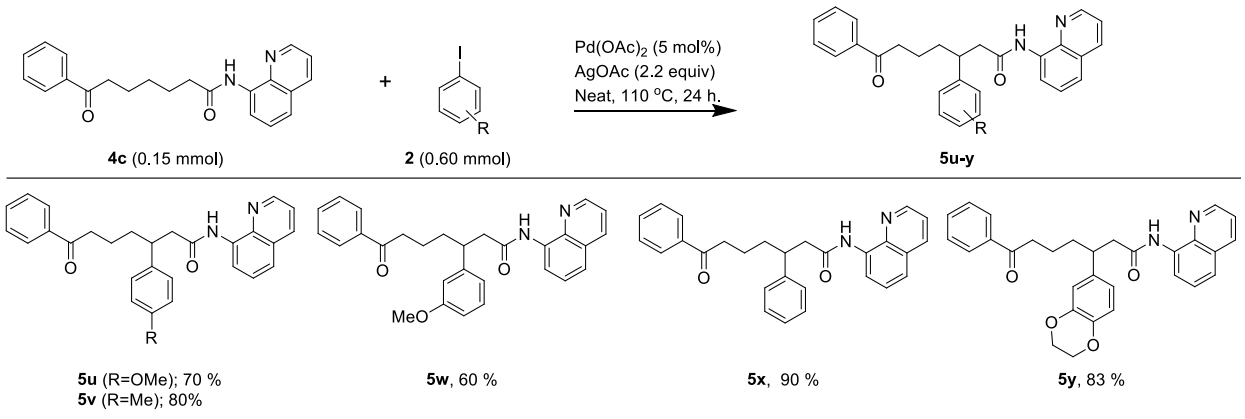
Table 3. Pd(II)-catalyzed 8-aminoquinoline-directed β-C(sp^3)-H arylation of ε-keto carboxamide **4b** with different aryl iodides.



Next, it was envisaged to extend the substrate scope and ε-keto carboxamide **4b** was assembled and treated with different aryl iodides. Accordingly, the ε-keto carboxamide **4b** (0.15 mmol) was treated with aryl iodides containing electron-donating substituents e.g., OMe, Me, and Et at the *para* position and PhI in the presence of 5 mol% of $Pd(OAc)_2$ catalyst and AgOAc additive at 110 °C in neat condition. These reactions afforded the corresponding β-C-H arylated products **5j-m** in 57-78% yields (Table 3). Further, the ε-keto carboxamide **4b** was treated with aryl iodides containing electron-donating and electron-withdrawing substituents e.g., Me, OMe, Br and F at the *meta* position and disubstituted aryl iodides in the presence of 5 mol% of $Pd(OAc)_2$ catalyst and AgOAc additive at 110 °C in neat condition, which also afforded the corresponding β-C-H arylated products **5n-t** in 55-80% yields (Table 3).

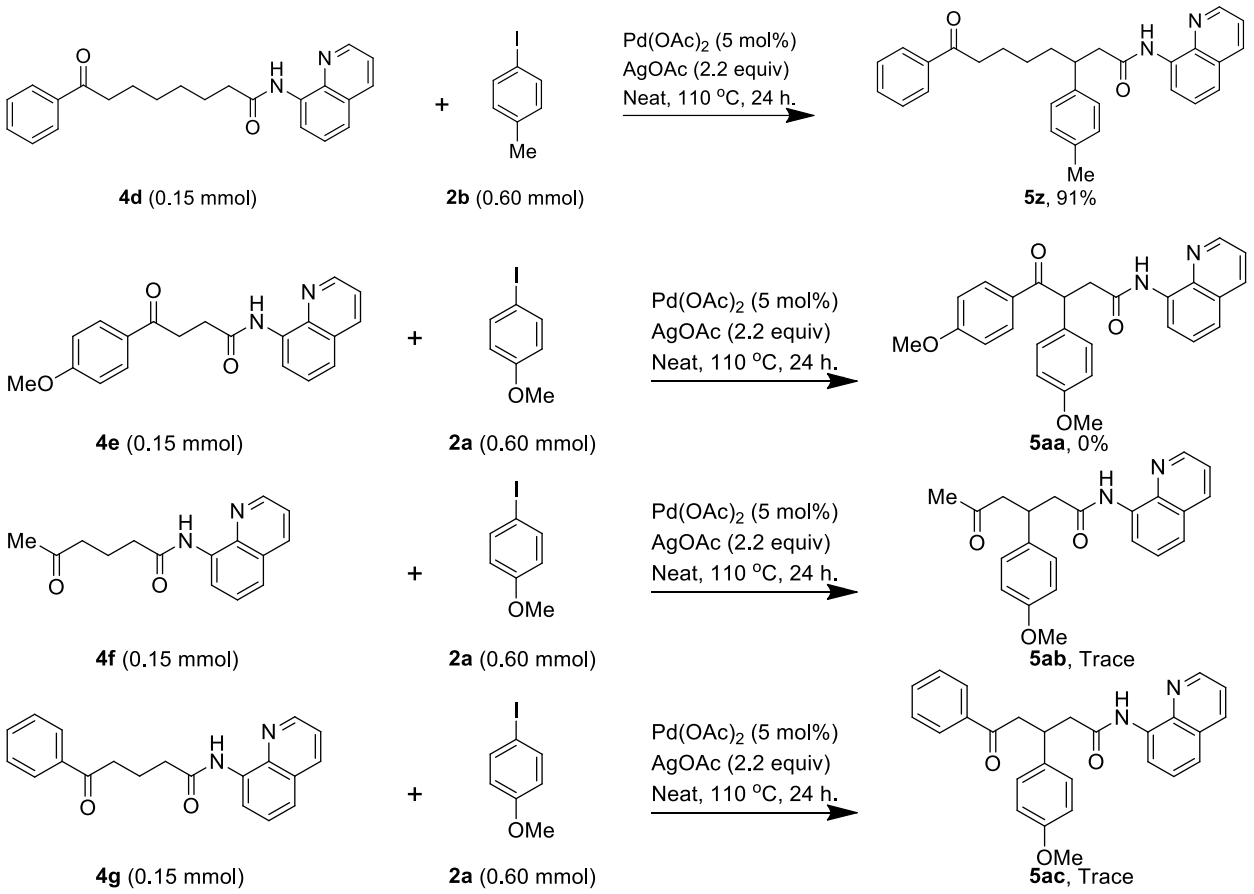
After investigating the substrate scope using ε-keto carboxamides **4a,b**, next the ζ-keto carboxamide **4c** was assembled and subjected to the Pd(II)-catalyzed C-H arylation with different aryl iodides (Table 4). Accordingly, the ζ-keto carboxamide **4c** (0.15 mmol) was treated with aryl iodides containing electron-donating substituents e.g., OMe and Me at the *para* or *meta* position, PhI and disubstituted aryl iodide in the presence of 5 mol% of $Pd(OAc)_2$ catalyst and AgOAc additive at 110 ^oC in neat condition. These reactions afforded the corresponding β-C-H arylated products **5u-y** in 60-90% yields (Table 4).

Table 4. Pd(II)-catalyzed 8-aminoquinoline-directed β-C(sp^3)-H arylation of ζ-keto carboxamide **4c** with different aryl iodides.



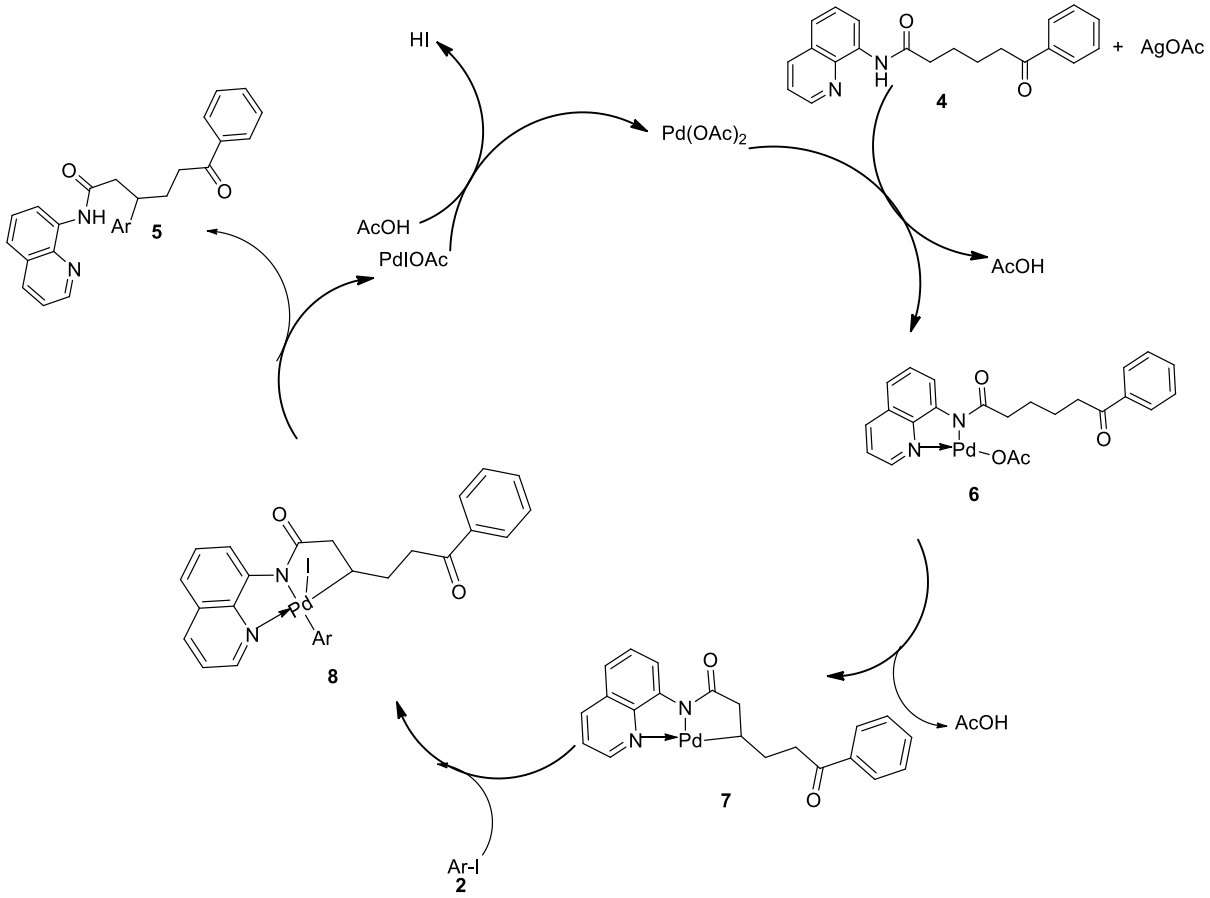
To further elaborate the substrate scope of this protocol involving the Pd(II)-catalyzed directed β-C(sp^3)-H arylation of keto carboxamides, the η-keto carboxamide **4d**, γ-keto carboxamide **4e** and δ-keto carboxamides **4f,g** were assembled. Then, the η-keto carboxamide **4d** (0.15 mmol) was treated with **2b** in the presence of 5 mol% of $Pd(OAc)_2$ catalyst and AgOAc additive at 110 ^oC in neat condition and this reaction afforded the product **5z** in 91% yield (Scheme 6). Finally, the γ-keto carboxamide **4e** or δ-keto carboxamides **4f,g 4d** (0.15 mmol) were treated with **2a** in the presence of 5 mol% of $Pd(OAc)_2$ catalyst and AgOAc additive at 110 ^oC in neat condition. Notably, the β-C(sp^3)-H arylation of keto carboxamides **4e-g** were not fruitful. While an exact reason for the failure of the reactions involving keto carboxamides **4e-g** is not known at this stage, however, it is assumed that the chelation and palladacycle formation process involving the activation of the β-C(sp^3)-H bond are perhaps disturbed by the keto group present in the keto carboxamides **4e-g**. Accordingly, the corresponding C-H activation and functionalization did not occur to give the corresponding C-H arylated products **5aa-ac** (Scheme 6). This observation is contrary to the substrates ε-keto carboxamide **4a,b**, ζ-keto carboxamide **4c** and η-keto carboxamide **4d,** which

underwent the activation of the β-C(sp^3)-H bond to afford the corresponding β-C(sp^3)-H arylated products (Tables 1-4). Given that the keto groups are relatively far away from the β-C(sp^3)-H bonds in in the keto carboxamides **4a-d**, it is assumed that the chelation and palladacycle formation process involving the activation of the β-C(sp^3)-H bond are perhaps not disturbed by the keto group present in the keto carboxamides **4a-d**.



Scheme 6. Pd(II)-catalyzed 8-aminoquinoline-directed β-C(sp^3)-H arylation of η-keto carboxamide **4d** and γ- keto carboxamide **4e**, δ-keto carboxamides **4f,g** with aryl iodide **2b and 2a** respectively.

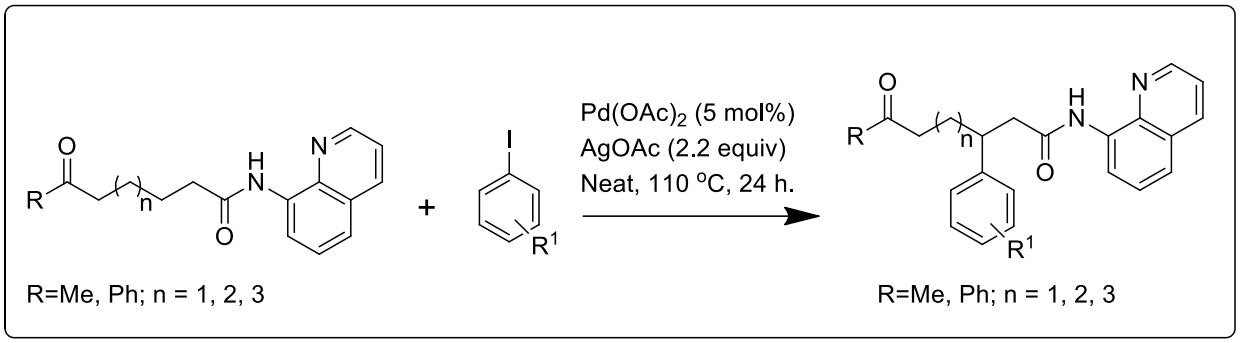
The plausible mechanism for Pd(II)-catalyzed 8-aminoquinoline-directed β-C(sp^3)-H arylation of carboxamide **4** is described in scheme 7. The first step involves bidentate co-ordination of Pd-catalyst with substrate **4** provides transition state **6**. Next, the C(sp^3)-H activation at β-carbon affords **7**, which further undergoes oxidative addition with aryl iodide provides Pd(IV) species **8**. Then the reductive elimination gives the β-arylated carboxamide **5**.



Scheme 7. A Plausible Mechanism for the Pd-Catalyzed β-arylation of carboxamide **4**.

Summary

In summary, chapter 4 reported the Pd(II)-catalyzed bidentate directing group, 8-aminoquinoline-directed β-C(sp^3)-H activation and arylation of ε-, ζ-, η-keto carboxamides. Synthesis of a library of β-C(sp^3)-H arylated/functionalized ε-, ζ-, η-keto carboxamides was shown. The reaction condition does not employ any solvent and the Pd(II)-catalyzed 8-aminoquinoline-directed β-C(sp^3)-H arylation of ε-, ζ-, η-keto carboxamides were performed in neat condition. Given that the keto carboxylic acid derivatives are important synthetic building blocks, the work shown here is although premature, however it will be a contribution to the library of β-arylated keto carboxylic acid derivatives.



General. Melting points are uncorrected. IR spectra of compounds were recorded as thin films or KBr pellets using Perkin Elmer FT-IR spectrometer. ^{1}H and ^{13}C NMR spectra of compounds were recorded on Bruker 400 MHz and 100 MHz spectrometers respectively using TMS as an internal standard. Mass spectra were recorded using SYNAPT G2S High Definition Mass Spectrometer. Column chromatography was carried out using silica gel 100-200 mesh. Reactions were performed in anhydrous solvent under a nitrogen atmosphere. Solutions were dried using anhydrous Na_2SO_4. Thin layer chromatography analysis was performed on silica gel plates and components were visualized by observation under iodine. Isolated yields of all the compounds were reported.

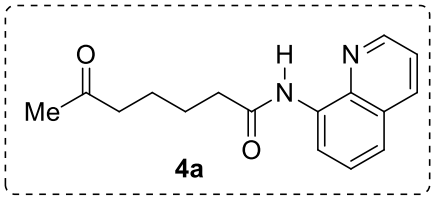
General Procedure for preparation of carboxamide 4a-g

To a solution of keto acid (10 mmol) in dry dichloromethane (30 mL), 1-hydroxy benzotriazole hydrate (11 mmol), and 1,3-dicyclohexylcarbodiimide (11 mmol) were added at 0 ^{o}C under nitrogen atmosphere. The suspension was warmed to room temperature and stirred for 1h. Then 8-amino quinoline (10 mmol) was added and mixture was stirred for 12 -15 h at room temperature. After this period, the resulting suspension was filtered through celite, extracted with chloroform (3x20 mL) and washed with brine solution. Then the filtrate was evaporated. The crude reaction mixture was purified by silica gel column (100-200 mesh, eluent; EtOAc: hexane) to afford the corresponding Carboxamides **4a-g**.

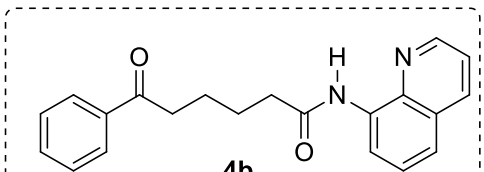
General Procedure Palladium-Catalyzed β-C(sp^3)-H Arylation on ε-, ζ-, η-Keto Acids.

Carboxamide **4a-g** (0.15 mmol), $Pd(OAc)_2$ (2.3 mg, 5 mol %), aryl iodide (0.60 mmol), AgOAc (2.2 equivalents) was heated at 110 ^{o}C, for 24 h under nitrogen atmosphere. After the reaction period, the reaction mixture was diluted with EtOAc and concentrated in vacuum and purification of the resulting reaction mixture by column chromatography silica gel furnished the corresponding C-H arylated products **5a-z**.

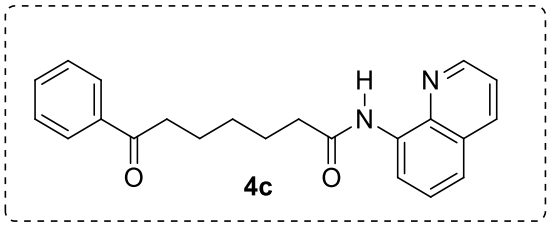
6-Oxo-*N*-(quinolin-8-yl)heptanamide (4a): Following the general procedure described above, **4a** was obtained after purification by column chromatography on silica gel (EtOAc:hexane = 25:75); Rf = 0.6 (EtOAc : Hex = 30:70); as colorless solid; Yield: 81% (2187 mg); mp 102 – 104 ^{o}C; IR (KBr): 3350, 2933, 1712, 1681, 1525 cm^{-1} ; ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.82 (s, 1H), 8.82 (dd, 1H, J_1 = 4.2 Hz, J_2 = 1.6 Hz), 8.78 (dd, 1H, J_1 = 7.2 Hz, J_2 = 1.7 Hz), 8.17 (dd, 1H, J_1 = 8.2 Hz, J_2 = 1.4 Hz), 7.56 – 7.45 (m, 3H), 2.60 (t, 2H, J = 7.1 Hz), 2.53 (t, 2H, J = 7.4 Hz), 2.16 (s, 3H), 1.87 – 1.71 (m ,4H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 208.8, 171.4, 148.2, 138.3, 136.4, 134.5, 127.9, 127.4, 121.6, 121.5, 116.4, 43.4, 37.9, 30.0, 25.0, 23.3; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{16}H_{19}N_2O_2$: 271.1447; found: 271.1440.



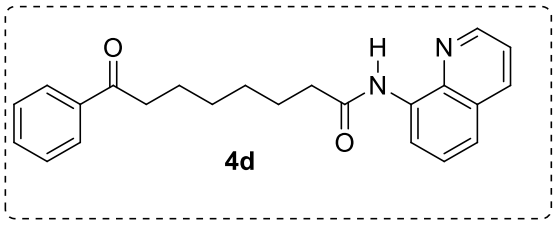
6-Oxo-6-phenyl-N-(quinolin-8-yl)hexanamide (4b): Following the general procedure described above, **4b** was obtained after purification by column chromatography on silica gel (EtOAc:hexane = 30:70); Rf = 0.5 (EtOAc : Hex = 30:70); as colorless solid; Yield:72% (2390mg); mp 94 – 96 ^{o}C; IR (KBr): 3353, 3056, 1682, 1596, 1524 cm^{-1} ; ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.85 (s, 1H), 8.82 (dd, 1H, J_1 = 4.2 Hz, J_2 = 1.6 Hz), 8.80 (dd, 1H, J_1 = 7.2 Hz, J_2 = 1.5 Hz), 8.18 (dd, 1H, J_1 = 8.2 Hz, J_2 = 1.5 Hz), 7.98 (d, 2H, J = 7.3 Hz), 7.58 – 7.45 (m, 6H), 3.09 (t, 2H, J = 6.9 Hz), 2.66 (t, 2H, J = 7.0 Hz), 1.95 – 1.93 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 200.0, 171.4, 148.2, 138.3, 136.9, 136.4, 134.5, 133.0, 128.6, 128.1, 127.9, 127.4, 121.6, 121.4, 116.4, 38.3, 38.0, 25.3, 23.8; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{21}H_{21}N_2O_2$: 333.1603; found: 333.1589.



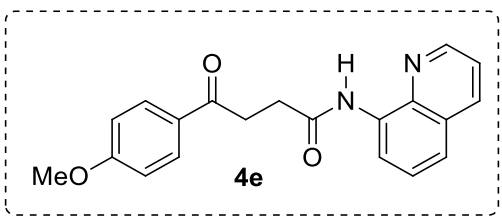
7-Oxo-7-phenyl-N-(quinolin-8-yl)heptanamide (4c): Following the general procedure described above, **4c** was obtained after purification by column chromatography on silica gel (EtOAc:hexane = 30:70); Rf = 0.5 (EtOAc : Hex = 30:70); as colorless solid; Yield: 89% (3079 mg); mp 98 – 100 ^{o}C; IR (KBr): 3356, 2936, 1682, 1525 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.86 (s, 1H), 8.83 – 8.79 (m, 2H), 8.19 (t, 1H, J = 8.1 Hz), 7.99 (t, 2H, J = 8.1 Hz), 7.58 – 7.47 (m, 6H), 3.05 (q, 2H, J = 8.0 Hz), 2.64 (q, 2H, J = 8.0 Hz), 1.95 – 1.82 (m, 4H), 1.60 – 1.53 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 200.3, 171.7, 148.2, 138.3, 137.0, 136.4, 134.5, 133.0, 128.6, 128.1, 127.9, 127.5, 121.6, 121.4, 116.4, 38.4, 38.0, 29.0, 25.5, 24.0.



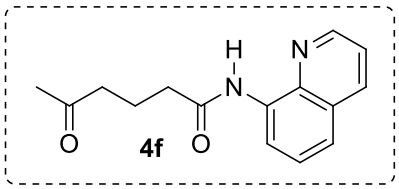
8-Oxo-8-phenyl-N-(quinolin-8-yl)octanamide (4d) : Following the general procedure described above, **4d** was obtained after purification by column chromatography on silica gel (EtOAc:hexane = 30:70); Rf = 0.5 (EtOAc : Hex = 30:70); as colorless solid; Yield: 94%; mp 70 – 72 ^{o}C; IR (KBr): 3352, 2935, 1682, 1524 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.83 (s, 1H), 8.83 – 8.80 (m, 2H), 8.18 (d, 1H, *J* = 8.3 Hz), 7.97 (d, 2H, *J* = 8.3 Hz), 7.59 – 7.45 (m, 6H), 3.00 (t, 2H, *J* = 7.5 Hz), 2.60 (t, 2H, *J* = 7.6 Hz), 1.89 – 1.76 (m, 4H), 1.52-1.50 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 200.5, 171.8, 148.2, 138.3, 137.0, 136.4, 134.5, 132.9, 128.6, 128.1, 127.9, 127.5, 121.6, 121.4, 116.4, 38.5, 38.2, 29.1, 25.5, 24.2; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{23}H_{25}N_2O_2$:361.1916; found: 361.1901.



4-Oxo-4-phenyl-N-(quinolin-8-yl)butanamide (4e) : Following the general procedure described above, **4e** was obtained after purification by column chromatography on silica gel (EtOAc:hexane = 40:50); Rf = 0.3 (EtOAc : Hex = 30:70); as colorless solid; Yield: 98% (3273 mg); mp 136 - 138 ^{o}C; IR (KBr): 3355, 2932, 1675, 16000, 1526 cm^{-1} ; ^{1}H NMR (400 MHz, $CDCl_3$): δ 10.2 (s, 1H), 8.84 (dd, 1H, J_1 = 4.2 Hz, J_2 = 1.6 Hz), 8.76 (dd, 1H, J_1 = 6.9 Hz, J_2 = 2.0 Hz), 8.16 (dd, 1H, J_1 = 8.3 Hz, J_2 = 1.7 Hz), 8.03 (d, 2H, *J* = 8.9 Hz), 7.55 – 7.45 (m, 3H), 6.95 (d, 2H, *J* = 8.9 Hz), 3.88 (s, 3H), 3.48 (t, 2H, *J* = 6.8 Hz), 3.05 (t, 2H, *J* = 6.7 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 197.1, 170.8, 163.6, 148.2, 138.3, 136.3, 134.6, 130.4, 130.0, 127.9, 127.4, 121.6, 121.4, 116.4, 113.7, 55.5, 33.4, 31.8; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{20}H_{19}N_2O_3$: 335.1396; found: 335.1379.

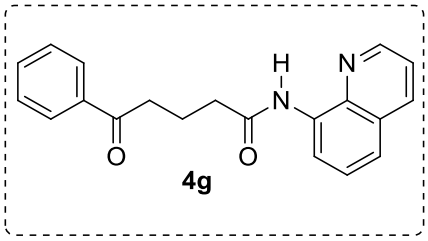


5-Oxo-N-(quinolin-8-yl)hexanamide (4f): Following the general procedure described above, **4f** was obtained after purification by column chromatography on silica gel (EtOAc:hexane = 55:45); Rf = 0.2 (EtOAc : Hex = 30:70); Yield: 78% (1996 mg); mp 67 – 69 ^{o}C; IR (KBr): 3351, 2938, 1713, 1683, 1526 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.76 (s, 1H), 8.74 – 8.70 (m, 2H), 8.08 (dd, 1H, J_1 = 8.3 Hz, J_2 = 1.6 Hz)), 7.49 – 7.36 (m, 3H), 2.56 (q, 4H, *J* = 7.2 Hz)), 2.11 (s, 3H), 2.07 – 2.00 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 208.4,



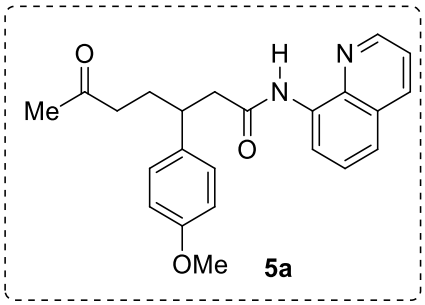
171.1, 148.2, 138.2, 136.3, 134.4, 127.9, 127.3, 121.6, 121.5, 116.3, 42.5, 36.7, 30.0, 19.4; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{15}H_{17}N_2O_2$: 257.1290; found: 257.1277.

5-Oxo-5-phenyl-N-(quinolin-8-yl)pentanamide (4g): Following the general procedure described above, **4g** was obtained after purification by column chromatography on silica gel (EtOAc:hexane = 30:70); Rf = 0.5 (EtOAc : Hex = 30:70); as colorless solid; Yield: 78% (248 mg); mp 91 – 93 ºC; IR (KBr): 3351, 3057, 1685, 1596, 1525 cm^{-1} ; ^1H NMR (400 MHz, $CDCl_3$): δ 9.86 (s, 1H), 8.80 (d, 2H, *J* = 5.4 Hz), 8.16 (dd, 1H, J_1 = 8.2 Hz, J_2 = 1.1 Hz), 8.00 (d, 2H, *J* = 7.7 Hz), 7.58 – 7.44 (m, 6H), 3.20 (t, 2H, *J* = 7.0 Hz), 2.73 (t, 2H, *J* = 7.2 Hz), 2.32 – 2.25 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 199.7, 171.2, 148.2, 138.3, 136.8, 136.4, 134.5, 133.1, 128.6, 128.1, 127.9, 127.4, 121.6, 121.5, 116.4, 37.6, 36.9, 20.0; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{20}H_{19}N_2O_2$: 319.1447; found: 319.1432.



4g

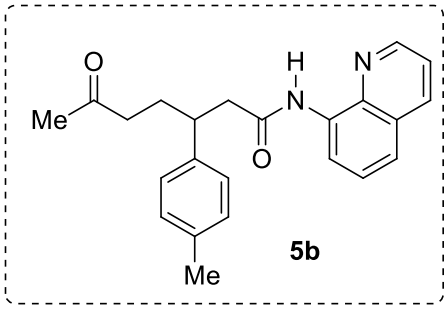
3-(4-Methoxyphenyl)-6-oxo-N-(quinolin-8-yl)heptanamide (5a): Following the general procedure described above, **5a** was obatined after purification by column chromatography on silica gel (EtOAc:hexane = 50:50); Rf = 0.5 (EtOAc : Hex = 30:70); as colorless solid; Yield: 73% (41 mg); mp 102 – 104 ºC; IR (KBr): 3350, 2933, 1712, 1681, 1525 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 9.68 (s, 1H), 8.76 (dd, 1H, J_1 = 4.2 Hz, J_2 = 1.6 Hz), 8.72 (dd, 1H, J_1 = 7.0 Hz, J_2 = 2.0 Hz), 8.13 (dd, 1H, J_1 = 8.3 Hz, J_2 = 1.6 Hz), 7.52 – 7.42 (m, 3H), 7.20 (d, 2H, *J* = 8.6 Hz), 6.84 (d, 2H, *J* = 8.7 Hz), 3.75 (s, 3H), 3.29 – 3.21 (m, 1H), 2.89 – 2.79 (m, 2H), 2.44 -2.36 (m, 1H), 2.31 – 2.23 (m, 1H), 2.16 – 2.06 (m, 1H), 2.05 (s, 3H), 1.97 – 1.88 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 208.7, 170.0, 158.3, 148.0, 138.2, 136.3, 135.1, 134.3, 128.5, 127.9, 127.3, 121.6, 121.5, 116.4, 114.1, 55.2, 46.0, 41.8, 41.1, 30.0, 29.9; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{23}H_{25}N_2O_3$: 377.1865; found: 377.1881.



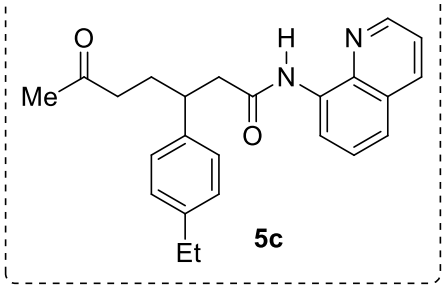
5a

6-Oxo-N-(quinolin-8-yl)-3-(p-tolyl)heptanamide (5b): Following the general procedure described above, **5b** was obtained after purification by column chromatography on silica gel (EtOAc:hexane = 30:70); Rf = 0.7 (EtOAc : Hex = 30:70); as colorless solid; Yield: 72% (39 mg); mp 70 – 72 ºC; IR (KBr): 3352, 2924, 1714, 1686, 1525 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 9.71 (s, 1H), 8.77 (dd, 1H, J_1 = 4.2 Hz, J_2 = 1.6 Hz), 8.73 (dd, 1H, J_1 = 7.0 Hz, J_2 = 2.0 Hz), 8.14

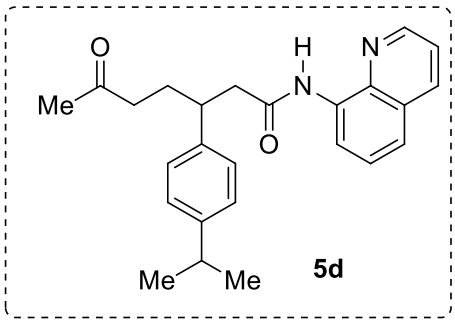
(dd, 1H, J_1 = 8.3 Hz, J_2 = 1.5 Hz), 7.52 – 7.42 (m, 3H), 7.18 (d, 2H, J = 8.0 Hz), 7.12 (d, 2H, J = 8.0 Hz), 3.30 – 3.23 (m, 1H), 2.86 (d, 2H, J = 7.4 Hz), 2.45 – 2.37 (m, 1H), 2.32 – 2.23 (m, 1H), 2.29 (s, 3H), 2.16 – 2.06 (m, 1H), 2.04 (s, 3H), 1.99 – 1.88 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 208.7, 170.0, 148.1, 140.1, 138.2, 136.3, 136.3, 134.4, 129.5, 127.9, 127.4, 127.3, 121.6, 121.5, 116.4, 45.8, 41.8, 41.5, 30.0, 29.8, 21.0; HRMS (ESI): *m/z* [M + H]$^+$ calcd for $C_{23}H_{25}N_2O_2$: 361.1916; found: 361.1900.



3-(4-Ethylphenyl)-6-oxo-N-(quinolin-8-yl)heptanamide (5c): Following the general procedure described above, **5c** was obtained after purification by column chromatography on silica gel (EtOAc:hexane = 30:70); Rf = 0.6 (EtOAc : Hex = 30:70); as colorless solid; Yield: 46% (26 mg); mp 87 – 89 ^{o}C; IR (KBr): 3351, 2963, 1714, 1687, 1525 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.71 (s, 1H), 8.77 (dd, 1H, J_1 = 4.2 Hz, J_2 = 1.9 Hz), 8.74 (dd, 1H, J_1 = 7.0 Hz, J_2 = 1.8 Hz), 8.14 (dd, 1H, J_1 = 8.2 Hz, J_2 = 1.6 Hz), 7.53 – 7.43 (m, 3H), 7.20 (d, 2H, J = 8.1 Hz), 7.14 (d, 2H, J = 8.0 Hz), 3.31 – 3.24 (m, 1H), 2.86 (d, 2H, J = 7.3 Hz), 2.60 (q, 2H, J = 7.6 Hz), 2.46 – 2.37 (m, 1H), 2.33 – 2.24 (m, 1H), 2.17 – 2.08 (m, 1H), 2.05 (s, 3H), 2.01 – 1.91 (m, 1H), 1.20 (t, 3H, J = 7.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 208.7, 170.1, 148.1, 142.6, 140.3, 138.2, 136.3, 134.4, 128.2, 127.9, 127.5, 127.3, 121.6, 121.5, 116.4, 45.8, 41.8, 41.5, 30.0, 29.8, 28.4, 15.4; HRMS (ESI): *m/z* [M + H]$^+$ calcd for $C_{24}H_{27}N_2O_2$: 375.2073; found: 375.2061.

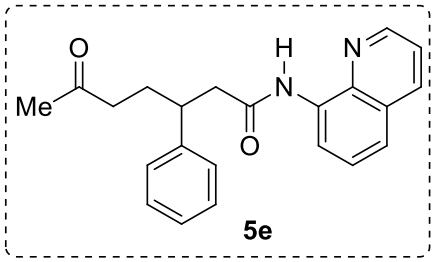


3-(4-Isopropylphenyl)-6-oxo-N-(quinolin-8-yl)heptanamide (5d): Following the general procedure described above, **5d** was obtained after purification by column chromatography on silica gel (EtOAc:hexane = 25:75); Rf = 0.8 (EtOAc : Hex = 30:70); as colorless solid; Yield: 81% (47 mg); mp 74 – 76 ^{o}C; IR (KBr): 3352, 2960, 1714, 1688, 1525 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.70 (s, 1H), 8.77 (dd, 1H, J_1 = 4.2 Hz, J_2 = 1.6 Hz), 8.74 (dd, 1H, J_1 = 7.1 Hz, J_2 = 1.8 Hz), 8.13 (dd, 1H, J_1 = 8.2 Hz, J_2 = 1.6 Hz), 7.52 – 7.41 (m, 3H), 7.20 (d, 2H, J = 8.2 Hz), 7.16 (d, 2H, J = 8.2 Hz), 3.31 – 3.24 (m, 1H), 2.86 (d, 2H, J = 7.3 Hz), 2.46 – 2.37 (m, 1H), 2.33 – 2.25 (m, 1H), 2.17 – 2.08 (m, 1H), 2.05 (s, 3H), 2.01 –

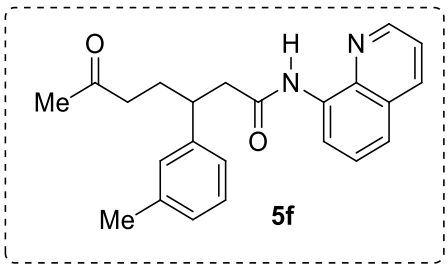


1.91 (m, 1H), 1.19 (d, 3H, J = 6.9 Hz), 1.19 (d, 3H, J = 6.9 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 208.8, 170.1, 148.1, 147.2, 140.5, 138.2, 136.3, 134.4, 127.9, 127.4, 127.3, 126.8, 121.6, 121.5, 116.4, 45.8, 41.8, 41.5, 33.6, 30.0, 29.8, 24.0, 23.9; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{25}H_{29}N_2O_2$: 389.2229; found: 389.2211.

6-Oxo-3-phenyl-N-(quinolin-8-yl)heptanamide (5e): Following the general procedure described above, **5e** was obtained after purification by column chromatography on silica gel (EtOAc:hexane = 30:70); Rf = 0.7 (EtOAc : Hex = 30:70); as colorless solid; Yield: 75% (39 mg); mp 70 – 72 ºC; IR (KBr): 3351, 2934, 1713, 1687, 1525 cm^{-1} ; ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.71 (s, 1H), 8.73 (dd, 1H, J_1 = 4.2 Hz, J_2 = 1.6 Hz), 8.60 (dd, 1H, J_1 = 6.8 Hz, J_2 = 2.1 Hz), 8.14 (dd, 1H, J_1 = 8.2 Hz, J_2 = 1.6 Hz), 7.53 – 7.42 (m, 3H), 7.34 – 7.30 (m, 4H), 7.23 – 7.20 (m, 1H), 3.33 – 3.27 (m, 1H), 2.88 (d, 2H, J = 7.4 Hz), 2.46 – 2.38 (m, 1H), 2.31 – 2.23 (m, 1H), 2.18 – 2.10 (m, 1H), 2.04 (s, 3H), 2.02 – 1.92 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 208.6, 169.9, 148.1, 143.2, 138.2, 136.3, 134.3, 128.8, 127.9, 127.6, 127.3, 126.8, 121.6, 121.5, 116.5, 45.7, 41.9, 41.7, 30.0, 29.8; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{22}H_{23}N_2O_2$: 347.1760; found: 347.1745.

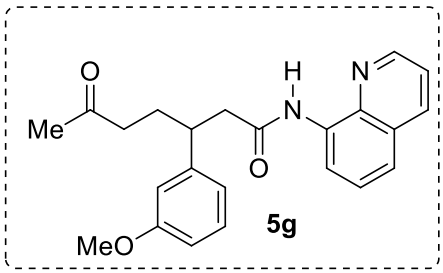


6-Oxo-N-(quinolin-8-yl)-3-(*m*-tolyl)heptanamide (5f): Following the general procedure described above, **5f** was obtained after purification by column chromatography on silica gel (EtOAc:hexane = 30:70); Rf = 0.6 (EtOAc : Hex = 30:70); as colorless solid; Yield: 78% (42 mg); mp 102 – 104 ºC; IR (KBr): 3351, 2925, 1712, 1686, 1524 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.70 (s, 1H), 8.74 (dd, 1H, J_1 = 4.2 Hz, J_2 = 1.6 Hz), 8.73 (dd, 1H, J_1 = 7.0 Hz, J_2 = 1.9 Hz), 8.14 (dd, 1H, J_1 = 8.3 Hz, J_2 = 1.6 Hz), 7.53 – 7.42 (m, 3H), 7.20 (t, 1H, J = 7.5 Hz), 7.10 (s, 1H), 7.09 (d, 1H, J = 9.3 Hz), 7.01 (d, 1H, J = 7.5 Hz), 3.29 – 3.22 (m, 1H), 2.87 (d, 2H, J = 7.4 Hz), 2.48 – 2.38 (m, 1H), 2.32 (s, 3H), 2.31 – 2.24 (m, 1H), 2.16 – 2.08 (m, 1H), 2.05 (s, 3H), 2.00 – 1.91 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 208.7, 170.0, 148.1, 143.2, 138.3, 138.2, 136.3, 134.3, 128.6, 128.3, 127.9, 127.6, 127.3, 124.6, 121.6, 121.5, 116.4, 45.7, 41.8, 41.8, 30.0, 29.8, 21.5; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{23}H_{25}N_2O_2$: 361.1916; found: 361.1902.

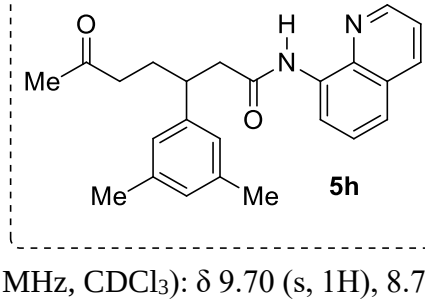


3-(3-Methoxyphenyl)-6-oxo-N-(quinolin-8-yl)heptanamide (5g): Following the general procedure described above, **5g** was obtained after purification by column chromatography on silica

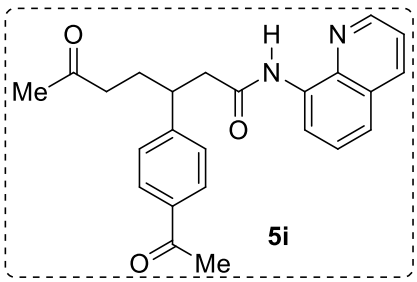
gel (EtOAc:hexane = 50:50); Rf = 0.6 (EtOAc : Hex = 30:70); as colorless solid; Yield: 66% (37 mg); mp 136 – 138 ^{o}C; IR (KBr): 3350, 2937, 1713, 1686, 1525 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.71 (s, 1H), 8.77 (dd, 1H, J_1 = 4.1 Hz, J_2 = 1.3 Hz), 8.73 (dd, 1H, J_1 = 6.9 Hz, J_2 = 2.0 Hz), 8.13 (d, 1H, J = 8.2 Hz), 7.52 – 7.42 (m, 3H), 7.22 (t, 1H, J = 7.9 Hz), 6.88 (d, 1H, J = 7.7 Hz), 6.83 (t, 1H, J = 2.2 Hz), 6.74 (dd, 1H, J_1 = 8.2 Hz, J_2 = 2.2 Hz), 3.78 (s, 3H), 3.31 – 3.24 (m, 1H), 2.87 (d, 2H, J = 7.3 Hz), 2.46 – 2.38 (m, 1H), 2.33 – 2.25 (m, 1H), 2.16 – 2.09 (m, 1H), 2.05 (s, 3H), 2.00 – 1.90 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 208.6, 169.9, 159.9, ,148.1, 144.9, 138.2, 136.3, 134.3, 129.8, 127.9, 127.3, 121.6, 121.5, 119.9, 116.4, 113.3, 112.0, 55.2, 45.7, 41.9, 41.7, 30.0, 29.7; HRMS (ESI): *m/z* [M + H]$^{+}$ calcd for $C_{23}H_{25}N_2O_3$: 377.1865; found: 377.1854.



3-(3,5-Dimethylphenyl)-6-oxo-N-(quinolin-8-yl)heptanamide (5h): Following the general procedure described above, **5h** was obtained after purification by column chromatography on silica gel (EtOAc:hexane = 30:70); Rf = 0.6 (EtOAc : Hex = 30:70); as colorless solid; Yield: 39% (22 mg); mp 110 – 112 ^{o}C; IR (KBr): 3352, 2919, 1713, 1687, 1525 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.70 (s, 1H), 8.78 (dd, 1H, J_1 = 4.2 Hz, J_2 = 1.6 Hz), 8.74 (dd, 1H, J_1 = 7.0 Hz, J_2 = 1.8 Hz), 8.15 (dd, 1H, J_1 = 8.3 Hz, J_2 = 1.5 Hz), 7.54 – 7.43 (m, 3H), 6.89 (s, 2H), 6.83 (s, 1H), 3.25 – 3.18 (m, 1H), 2.85 (d, 2H, J = 6.7 Hz), 2.47 – 2.37 (m, 1H), 2.28 (s, 6H), 2.33 – 2.25 (m, 1H), 2.15 – 2.08 (m, 1H), 2.06 (s, 3H), 1.99 – 1.90 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 208.8, 170.1, 148.0, 143.1, 138.3, 138.1, 136.3, 134.4, 128.5, 127.9, 127.3, 125.3, 121.6, 121.4, 116.4, 45.8, 41.9, 41.8, 30.0, 29.8, 21.4; HRMS (ESI): *m/z* [M + H]$^{+}$ calcd for $C_{24}H_{27}N_2O_2$: 375.2073; found: 375.2055.

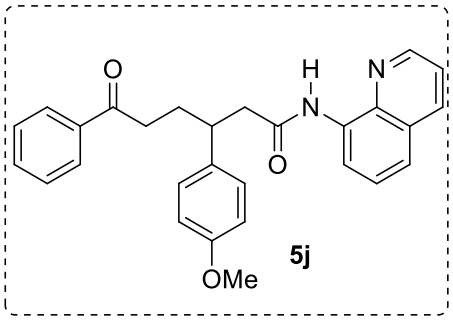


3-(4-Acetylphenyl)-6-oxo-N-(quinolin-8-yl)heptanamide (5i): Following the general procedure described above, **5i** was obtained after purification by column chromatography on silica gel (EtOAc:hexane = 75:25); Rf = 0.2 (EtOAc : Hex = 30:70); as colorless solid; Yield: 34% (20 mg); IR (KBr): cm^{-1} ; ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.69 (s, 1H), 8.76 (dd, 1H, J_1 = 4.2 Hz, J_2 = 1.6 Hz), 8.69 (dd, 1H, J_1 =

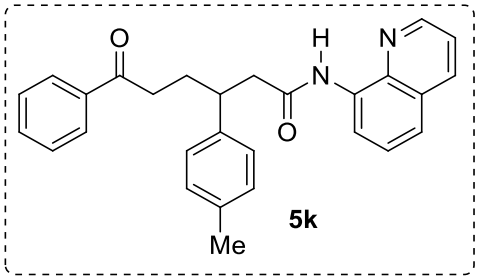


5.8 Hz, J_2 = 3.2 Hz), 8.14 (dd, 1H, J_1 = 8.3 Hz, J_2 = 1.5 Hz), 7.90 (d, 2H, J = 8.3 Hz), 7.53 – 7.43 (m, 3H), 7.39 (d, 2H, J = 8.3 Hz), 3.43 – 3.36 (m, 1H), 2.96 – 2.84 (m, 2H), 2.55 (s, 3H), 2.46 – 2.38 (m, 1H), 2.30 – 2.13 (m, 2H), 2.06 (s, 3H), 2.04 – 1.95 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 208.1, 197.8, 169.4, 149.0, 148.1, 138.2, 136.4, 135.9, 134.1, 128.9, 127.9, 127.3, 121.6, 116.5, 45.2, 41.8, 41.5, 30.0, 29.5, 26.6.

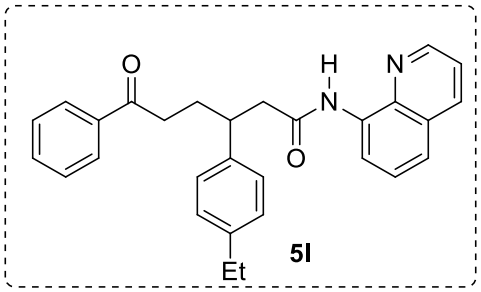
3-(4-Methoxyphenyl)-6-oxo-6-phenyl-N-(quinolin-8-yl)hexanamide (5j): Following the general procedure described above, **5j** was obtained after purification by column chromatography on silica gel (EtOAc:hexane = 50:50); Rf = 0.5 (EtOAc : Hex = 30:70); as colorless solid; Yield: 76% (50 mg); mp 100 – 102 ^{o}C; IR (KBr): 3351, 2933, 1683, 1524 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.71 (s, 1H), 8.77 (dd, 1H, J_1 = 4.2 Hz, J_2 = 1.6 Hz), 8.74 (dd, 1H, J_1 = 7.0 Hz, J_2 = 1.9 Hz), 8.13 (dd, 1H, J_1 = 8.3 Hz, J_2 = 1.6 Hz), 7.85-7.83 (m, 2H), 7.53 – 7.38 (m, 6H), 7.26 (d, 2H, J = 8.6 Hz), 6.86 (d, 2H, J = 8.7 Hz), 3.43 – 3.35 (m, 1H), 3.76, (s, 3H), 3.01 – 2.77 (m, 4H), 2.33 – 2.24 (m, 1H), 2.17 – 2. 06 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 200.0, 170.1, 158.3, 148.1, 138.2, 136.8, 136.3, 135.2, 134.4, 132.9, 128.6, 128.5, 128.0, 127.9, 127.3, 121.6, 121.5, 116.4, 114.2, 55.2, 46.1, 41.4, 36.7, 30.5; HRMS (ESI): *m/z* [M + H]$^+$ calcd for $C_{28}H_{27}N_2O_3$: 439.2022; found: 439.2004.



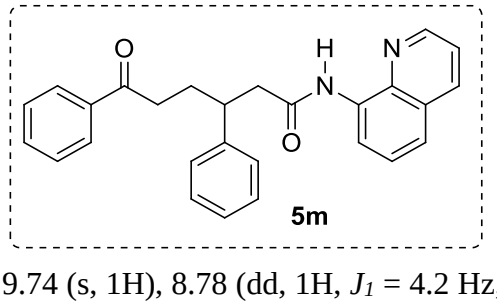
6-Oxo-6-phenyl-N-(quinolin-8-yl)-3-(*p*-tolyl)hexanamide (5k): Following the general procedure described above, **5k** was was obtained after purification by column chromatography on silica gel (EtOAc:hexane = 30:70); Rf = 0.7 (EtOAc : Hex = 30:70); as colorless solid; Yield: 78% (49 mg); mp 118 – 120 ^{o}C; IR (KBr): 3351, 2925, 1683, 1524 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.73 (s, 1H), 8.78 (dd, 1H, J_1 = 4.2 Hz, J_2 = 1.6 Hz), 8.74 (dd, 1H, J_1 = 7.0 Hz, J_2 = 2.0 Hz), 8.15 (dd, 1H, J_1 = 8.3 Hz, J_2 = 1.6 Hz), 7.85-7.83 (m, 2H), 7.54 – 7.38 (m, 6H), 7.24 (d, 2H, J = 8.0 Hz), 7.13 (d, 2H, J = 7.9 Hz), 3.44 – 3.36 (m, 1H), 3.02 – 2.91 (m, 3H), 2.85 – 2.77 (m, 1H), 2.30 (s, 3H), 2.33 – 2.25 (m, 1H), 2.20 – 2.12 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 200.0, 170.1, 148.0, 140.2, 138.3, 136.8, 136.3, 134.4, 132.9, 129.5, 128.5, 128.0, 127.9, 127.5, 127.4, 121.6, 121.4, 116.5, 46.0, 41.7, 36.8, 30.4, 21.1; HRMS (ESI): *m/z* [M + H]$^+$ calcd for $C_{28}H_{27}N_2O_2$: 423.2073; found: 423.2062.



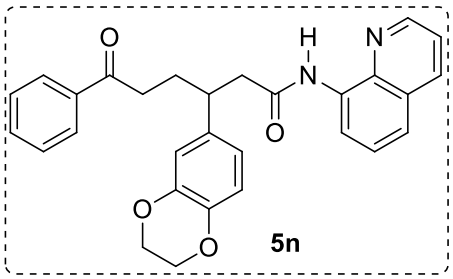
3-(4-Ethylphenyl)-6-oxo-6-phenyl-N-(quinolin-8-yl)hexanamide (5l): Following the general procedure described above, **5l** was obtained after purification by column chromatography on silica gel (EtOAc:hexane = 30:70); Rf = 0.7 (EtOAc : Hex = 30:70); as colorless solid; Yield: 63% (41 mg); mp 84 – 86 ^{o}C; IR (KBr): 3351, 2930, 1683, 1524 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.73 (s, 1H), 8.77 – 8.73 (m, 2H), 8.13 (dd, 1H, J_1 = 8.3 Hz, J_2 = 1.6 Hz), 7.84 (d, 2H, J = 7.2 Hz), 7.52 – 7.37 (m, 6H), 7.28-7.26 (m, 2H), 7.15 (d, 2H, J = 8.0 Hz), 3.45 – 3.38 (m, 1H), 3.03 – 2.94 (m, 1H), 2.93 (d, 2H, J = 7.3 Hz), 2.86 – 2.76 (m, 1H), 2.60 (q, 2H, J = 7.6 Hz), 2.34 – 2.24 (m, 1H), 2.22 – 2.11 (m, 1H), 1.19 (t, 3H, J = 7.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 200.0, 170.1, 148.1, 142.6, 140.5, 138.2, 136.8, 136.3, 134.4, 132.9, 128.5, 128.3, 128.0, 127.9, 127.5, 127.3, 121.6, 121.5, 116.4, 46.0, 41.7, 36.8, 30.4, 28.4, 15.5; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{29}H_{29}N_2O_2$: 437.2229; found: 437.2214.



6-Oxo-3,6-diphenyl-N-(quinolin-8-yl)hexanamide (5m): Following the general procedure described above, **5m** was obtained after purification by column chromatography on silica gel (EtOAc:hexane = 30:70); Rf = 0.7 (EtOAc : Hex = 30:70); as colorless solid; Yield: 57% (35 mg); mp 154 – 156 ^{o}C; IR (KBr): 3350, 2930, 1683, 1524 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.74 (s, 1H), 8.78 (dd, 1H, J_1 = 4.2 Hz, J_2 = 1.6 Hz), 8.74 (dd, 1H, J_1 = 6.9 Hz, J_2 = 2.0 Hz), 8.14 (dd, 1H, J_1 = 8.3 Hz, J_2 = 1.6 Hz), 7.84 (d, 2H, J = 7.2 Hz), 7.53 – 7.31 (m, 10H), 7.24 – 7.20 (m, 1H), 3.47 – 3.41 (m, 1H), 3.03 – 2.93 (m, 3H), 2.85 – 2.76 (m, 1H), 2.36 – 2.27 (m, 1H), 2.22 – 2.12 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 199.9, 169.9, 148.1, 143.3, 138.2, 136.8, 136.3, 134.3, 132.9, 128.8, 128.5, 128.0, 127.9, 127.6, 127.3, 126.8, 121.6, 121.5, 116.5, 45.8, 42.1, 36.7, 30.4; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{27}H_{25}N_2O_2$: 409.1916; found: 409.1901.

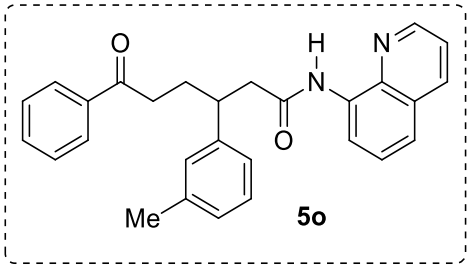


3-(2,3-Dihydrobenzo[b][1,4]dioxin-6-yl)-6-oxo-6-phenyl-N-(quinolin-8-yl)hexanamide (5n): Following the general procedure described above, **5n** was obtained after purification by column chromatography on silica gel (EtOAc:hexane = 70:30); Rf = 0.3 (EtOAc : Hex = 30:70); as colorless solid; Yield: 80% (56 mg); mp 130 – 132 ^{o}C; IR (KBr): 3349, 2931, 1682, 1525 cm^{-1}; ^{1}H NMR



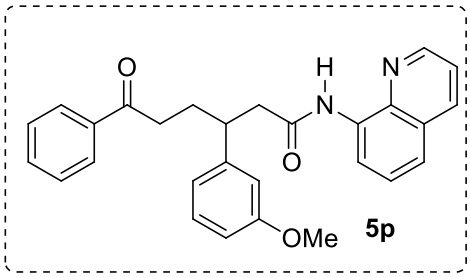
(400 MHz, $CDCl_3$): δ 9.72 (s, 1H), 8.78 (dd, 1H, J_1 = 4.2 Hz, J_2 = 1.6 Hz), 8.74 (dd, 1H, J_1 = 7.0 Hz, J_2 = 1.8 Hz), 8.13 (dd, 1H, J_1 = 8.3 Hz, J_2 = 1.6 Hz), 7.87-7.85 (m, 2H), 7.54-7.38 (m, 6H), 6.85-6.81 (m, 3H), 4.20 (s, 4H), 3.35 – 3.28 (m, 1H), 3.01 – 2.93 (m, 1H), 2.88 (d, 2H, *J* = 7.4 Hz), 2.85 – 2.78 (m, 1H), 2.30 – 2.21 (m, 1H), 2.14 – 2.05 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 200.0, 170.0, 148.1, 143.6, 142.3, 138.2, 136.8, 136.6, 136.3, 134.4, 132.9, 128.5, 128.0, 127.8, 127.4, 121.6, 121.5, 120.6, 117.4, 116.5, 116.2, 64.3, 64.3, 46.0, 41.5, 36.7, 30.5; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{29}H_{27}N_2O_4$: 467.1971; found: 467.1955.

6-Oxo-6-phenyl-N-(quinolin-8-yl)-3-(*m*-tolyl)hexanamide (5o): Following the general procedure described above, **5o** was obtained after purification by column chromatography on silica gel (EtOAc:hexane = 30:70); Rf = 0.7 (EtOAc : Hex = 30:70); as colorless solid; Yield: 79% (50 mg); mp 116 – 118 °C; IR (KBr): 3351, 2925, 1683, 1524 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 9.73 (s, 1H), 8.77 (dd, 1H, J_1 = 4.2 Hz, J_2 = 1.6 Hz), 8.75 (dd, 1H, J_1 = 7.1 Hz, J_2 = 1.8 Hz), 8.14 (dd, 1H, J_1 = 8.3 Hz, J_2 = 1.6 Hz), 7.86-7.84 (m, 2H), 7.53 – 7.38 (m, 6H), 7.23 – 7.14 (m, 3H), 7.02 (d, 1H, *J* = 7.5 Hz), 3.44 – 3.36 (m, 1H), 3.03 – 2.95 (m, 1H), 2.93 (d, 2H, *J* = 7.4 Hz), 2.85 – 2.77 (m, 1H), 2.34 – 2.26 (m, 1H), 2.32 (s, 3H), 2.21 – 2.11 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 200.0, 170.1, 148.1, 143.3, 138.4, 138.2, 136.8, 136.3, 134.4, 132.9, 128.7, 128.5, 128.3, 128.0, 127.9, 127.6, 127.3, 124.7, 121.6, 121.5, 116.4, 45.9, 42.1, 36.8, 30.4, 21.5; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{28}H_{27}N_2O_2$: 423.2073; found: 423.2069.



5o

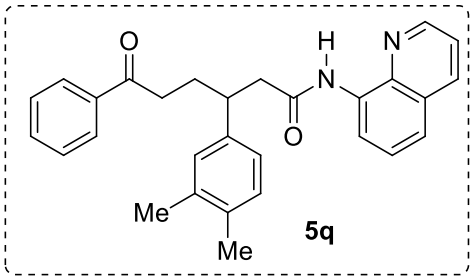
3-(3-Methoxyphenyl)-6-oxo-6-phenyl-N-(quinolin-8-yl)hexanamide (5p): Following the general procedure described above, **5p** was obtained after purification by column chromatography on silica gel (EtOAc:hexane = 50:50); Rf = 0.5 (EtOAc : Hex = 30:70); as colorless solid; Yield: 73% (80 mg); mp 92 – 94 °C; IR (KBr): 3350, 2936, 1682, 1524 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 9.74 (brs, 1H), 8.79 – 8.73 (m, 2H), 8.15 (t, 1H, *J* = 8.3 Hz), 7.86 (t, 2H, *J* = 8.3 Hz), 7.55 – 7.38 (m, 6H), 7.30 – 7.22 (m, 1H), 6.97-6.89 (m, 2H), 6.76 (t, 1H, *J* = 7.3 Hz), 3.79 (d, 3H, *J* = 9.5 Hz), 3.43 – 3.42 (m, 1H), 3.03 – 2.80 (m, 4H), 2.33 – 2.28 (m, 1H), 2.21 – 2.14 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 199.9, 169.9, 159.9, 148.1, 145.0, 145.0, 138.3, 138.3, 136.8, 136.3, 134.4, 132.9, 132.9, 129.8, 129.8, 128.5, 128.0, 127.9, 127.9, 127.3, 121.6, 121.5, 120.0,



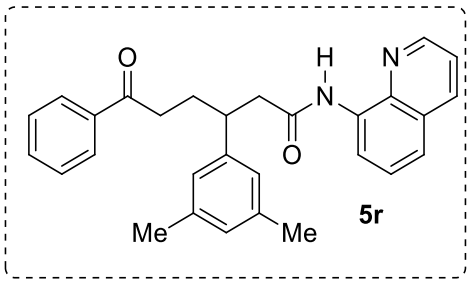
5p

116.5, 116.5, 113.3, 113.3, 112.1, 55.2, 45.9, 42.2, 36.7, 36.7, 30.3, 30.3; HRMS (ESI): *m/z* [M + H]$^+$ calcd for $C_{28}H_{27}N_2O_3$: 439.2022; found: 439.2012. (The more number of signals indicated that compound seems to be rotomer).

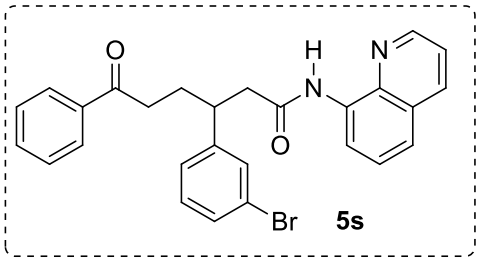
3-(3,4-Dimethylphenyl)-6-oxo-6-phenyl-N-(quinolin-8-yl)hexanamide (5q): Following the general procedure described above, **5q** was obtained after purification by column chromatography on silica gel (EtOAc:hexane = 40:60); Rf = 0.6 (EtOAc : Hex = 30:70); as colorless solid; Yield: 78% (51 mg); mp 136 – 138 ^{o}C; IR (KBr): 3351, 2936, 1683, 1524 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.72 (s, 1H), 8.78 – 8.74 (m, 2H), 8.14 (dd, 1H, J_1 = 8.2 Hz, J_2 = 1.5 Hz), 7.86-7.84 (m, 2H), 7.53 -7.37 (m, 6H), 7.10 (s, 1H), 7.08 (s, 2H), 3.40 – 3.33 (m, 1H), 3.02 – 2.94 (m, 1H), 2.91 (d, 2H, *J* = 7.4 Hz), 2.86 – 2.78 (m, 1H), 2.32 – 2.24 (m, 1H), 2.22 (s, 3H), 2.19 (s, 3H), 2.17 – 2.10 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 200.1, 170.2, 148.0, 140.7, 138.3, 136.9, 136.3, 134.9, 134.4, 132.9, 130.0, 128.8, 128.5, 128.0, 127.9, 127.4, 125.0, 121.5, 121.4, 116.5, 46.1, 41.8, 36.8, 30.4, 19.9, 19.4; HRMS (ESI): *m/z* [M + H]$^+$ calcd for $C_{29}H_{29}N_2O_2$: 437.2229; found: 437.2145.



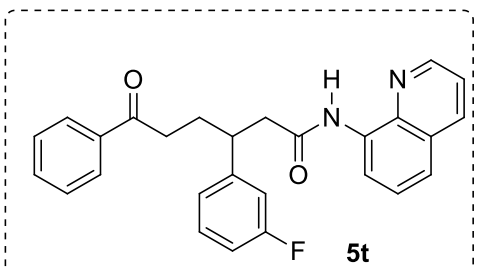
3-(3,5-Dimethylphenyl)-6-oxo-6-phenyl-N-(quinolin-8-yl)hexanamide (5r): Following the general procedure described above, **5r** was obtained after purification by column chromatography on silica gel (EtOAc:hexane = 30:70); Rf = 0.7 (EtOAc : Hex = 30:70); as colorless solid; Yield: 63% (41 mg); mp 156 – 158 ^{o}C; IR (KBr): 3351, 2918, 1682, 1524 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.72 (s, 1H), 8.78 – 8.74 (m, 2H), 8.13 (d, 1H, *J* = 8.2 Hz), 7.86-7.84 (m, 2H), 7.53 – 7.38 (m, 6H), 6.95 (s, 2H), 6.83 (s, 1H), 3.39 – 3.32 (m, 1H), 3.03 – 2.95 (m, 1H), 2.91 (d, 2H, *J* = 7.4 Hz), 2.86 – 2.77 (m, 1H), 2.33 – 2.24 (m, 1H), 2.28 (s, 6H), 2.20 – 2.10 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 200.1, 170.2, 148.0, 143.2, 138.3, 138.2, 136.9, 136.3, 134.4, 132.9, 128.5, 128.5, 128.0, 127.9, 127.3, 125.4, 121.6, 121.4, 116.4, 46.0, 42.0, 36.8, 30.4, 21.4; HRMS (ESI): *m/z* [M + H]$^+$ calcd for $C_{29}H_{29}N_2O_2$: 437.2229; found: 437.2214.



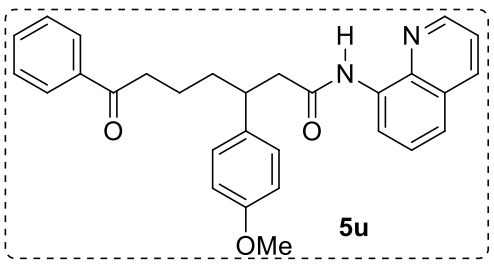
3-(3-Bromophenyl)-6-oxo-6-phenyl-N-(quinolin-8-yl)hexanamide (5s): Following the general procedure described above, **5s** was obtained after purification by column chromatography on silica gel (EtOAc:hexane = 35:65); Rf = 0.6 (EtOAc : Hex = 30:70);as colorless solid; Yield: 55% (40 mg); mp 108 – 110 ^{o}C; IR (KBr): 3351, 2938, 1683, 1526 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.72 (s, 1H), 8.80 – 8.70 (m, 1H), 8.72 (dd, 1H, J_1 = 6.4 Hz, J_2 = 2.3 Hz), 8.16 – 8.14 (m, 1H), 7.87 – 7.85 (m, 2H), 7.56 – 7.40 (m, 7H), 7.35 (d, 1H, J = 7.8 Hz), 7.28 – 7.27 (m, 1H), 7.18 (t, 1H, J = 7.7 Hz), 3.46 – 3.38 (m, 1H), 3.03 – 2.88 (m, 3H), 2.86 – 2.77 (m, 1H), 2.35 – 2.26 (m, 1H); 2.19 – 2.10 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 199.6, 169.4, 148.2, 145.9, 138.2, 136.7, 136.3, 134.2, 133.1, 130.5, 130.4, 130.0, 128.6, 128.0, 127.9, 127.3, 126.6, 123.0, 121.6, 121.6, 116.5, 45.6, 41.8, 36.5, 30.2; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{27}H_{24}BrN_2O_2$: 487.1021; found: 487.1006.



3-(3-Fluorophenyl)-6-oxo-6-phenyl-N-(quinolin-8-yl)hexanamide (5t): Following the general procedure described above, **5t** was obtained after purification by column chromatography on silica gel (EtOAc:hexane = 40:60); Rf = 0.6 (EtOAc : Hex = 30:70); as colorless solid; Yield: 56% (36 mg); mp 137 – 139 ^{o}C; IR (KBr): 3352, 2936, 1681, 1524 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.74 (brs, 1H), 8.80 – 8.71 (m, 2H), 8.18-8.14 (m, 1H), 7.88-7.85 (m, 2H), 7.57 – 7.38 (m, 6H), 7.32 – 7.25 (m, 1H), 7.16 – 7.06 (m, 2H), 6.94 – 6.88 (m, 1H), 3.47 – 3.46 (m, 1H), 3.03 – 2.78 (m, 4H), 2.34 – 2.28 (m, 1H), 2.19 – 2.12 (m, 1H); HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{27}H_{24}FN_2O_2$: 427.1822; found: 427.1808.

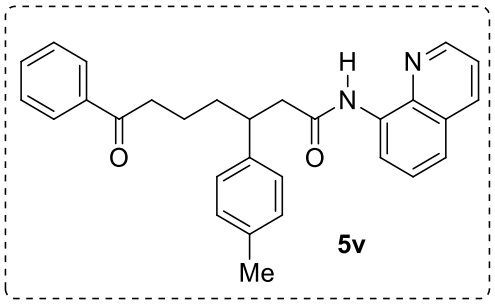


3-(4-Methoxyphenyl)-7-oxo-7-phenyl-N-(quinolin-8-yl)heptanamide (5u): Following the general procedure described above, **5u** was obtained after purification by column chromatography on silica gel (EtOAc:hexane = 45:55); Rf = 0.6 (EtOAc : Hex = 30:70); as colorless oil; Yield: 70% (47 mg); IR (KBr): 3352, 2933, 1683, 1524 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.69 (s, 1H), 8.77 – 8.73 (m, 2H), 8.13 (d, 1H, J = 8.2 Hz), 7.90 (d, 2H, J = 7.8 Hz), 7.55 – 7.23 (m, 6H), 7.29-7.24 (m, 2H), 6.84 (d, 2H, J = 7.2 Hz), 3.74 (s, 3H), 3.37 – 3.30 (m,

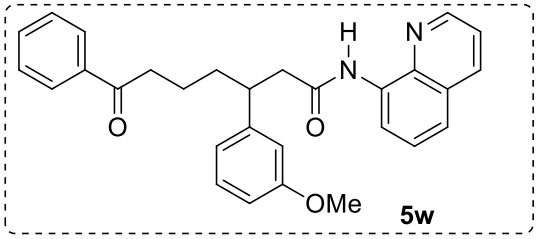


1H), 3.01 – 2.82 (m, 4H), 1.91 – 1.65 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 200.1, 170.4, 158.2, 148.0, 138.3, 136.9, 136.3, 135.7, 134.4, 132.9, 128.5, 128.5, 128.0, 127.9, 127.4, 121.6, 121.4, 116.5, 114.1, 55.2, 46.1, 41.7, 38.4, 35.7, 22.2; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{29}H_{29}N_2O_3$: 453.2178; found: 453.2162.

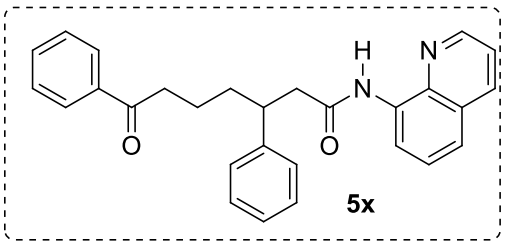
7-Oxo-7-phenyl-N-(quinolin-8-yl)-3-(p-tolyl)heptanamide (5v): Following the general procedure described above, **5v** was obtained after purification by column chromatography on silica gel (EtOAc:hexane = 30:70); Rf = 0.7 (EtOAc : Hex = 30:70); as colorless oil; Yield: 86% (56 mg); IR (KBr): 3352, 2926, 1684, 1524 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.71 (s, 1H), 8.77 – 8.74 (m, 2H), 8.14 (d, 1H, *J* = 8.2 Hz), 7.89 (d, 2H, *J* = 7.4 Hz), 7.53 – 7.41 (m, 6H), 7.22 (d, 2H, *J* = 7.4 Hz), 7.11 (d, 2H, *J* = 7.4 Hz), 3.37 – 3.32 (m, 1H), 3.00 – 2.86 (m, 4H), 2.29 (s, 3H), 1.92 – 1.63 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 200.1, 170.3, 148.0, 140.7, 138.3, 136.9, 136.3, 136.0, 134.4, 132.9, 129.5, 129.4, 129.2, 128.5, 128.0, 127.9, 127.4,127.4, 121.5, 121.4, 116.4, 45.9, 42.1, 38.4, 35.6, 22.2, 21.0; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{29}H_{29}N_2O_2$: 437.2229; found: 437.2208.



3-(3-Methoxyphenyl)-7-oxo-7-phenyl-N-(quinolin-8-yl)heptanamide (5w): Following the general procedure described above, **5w** was obtained after purification by column chromatography on silica gel (EtOAc:hexane = 50:50); Rf = 0.5 (EtOAc : Hex = 30:70); as colorless oil; Yield: 60% (40 mg); IR (KBr): 3351, 2936, 1683, 1524 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.71 (s, 1H), 8.77 – 8.74 (m, 2H), 8.15 (d, 1H, *J* = 8.2 Hz), 7.90 (d, 2H, *J* = 7.5 Hz), 7.55 – 7.41 (m, 6H), 7.22 (t, 1H, *J* = 7.8 Hz), 6.93 (d, 1H, *J* = 7.5 Hz), 6.89 (s, 1H), 6.73 (d, 1H, *J* = 8.2 Hz), 3.78 (s, 3H), 3.39 – 3.33 (m, 1H), 3.04 – 2.87 (m, 4H), 1.93 – 1.68 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 200.1, 170.2, 159.8, 148.1, 145.4, 138.3, 136.9, 136.3, 134.4, 132.9, 129.7, 128.5, 128.0, 127.9, 127.4, 121.6, 121.4, 120.0, 116.4, 113.3, 111.9, 55.1, 45.8, 42.6, 38.4, 35.5, 22.2; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{29}H_{29}N_2O_3$: 453.2178; found: 453.2160.

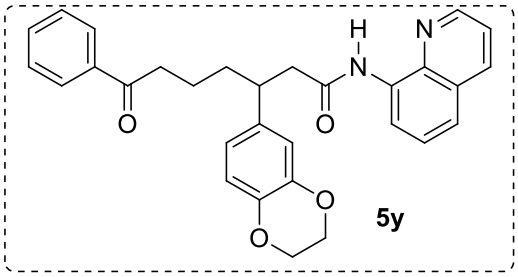


7-Oxo-3,7-diphenyl-N-(quinolin-8-yl)heptanamide (5x): Following the general procedure described above, **5x** was obtained after purification by column chromatography on silica gel (EtOAc:hexane = 30:70); Rf = 0.6 (EtOAc : Hex = 30:70); as colorless oil; Yield: 90% (58 mg);



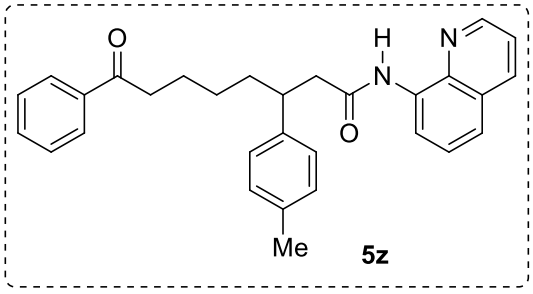
IR (KBr): 3352, 2933, 1684, 1524 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 9.72 (s, 1H), 8.76 – 8.74 (m, 2H), 8.13 (d, 1H, *J* = 8.2 Hz), 7.90 (d, 2H, *J* = 7.4 Hz), 7.55 – 7.18 (m, 11H), 3.41 – 3.36 (m, 1H), 3.01 – 2.88 (m, 4H), 1.92 – 1.67 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 200.1, 170.2, 148.1, 143.8, 138.3, 136.9, 136.3, 134.4, 132.9, 128.7, 128.5, 128.0, 127.9, 127.6, 127.4, 126.6, 121.6, 121.4, 116.4, 45.8, 42.5, 38.4, 35.6, 22.1; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{28}H_{27}N_2O_2$: 423.2073; found: 423.2057.

3-(2,3-Dihydrobenzo[b][1,4]dioxin-6-yl)-7-oxo-7-phenyl-N-(quinolin-8-yl)heptanamide (5y):



Following the general procedure described above, **5y** was obtained after purification by column chromatography on silica gel (EtOAc:hexane = 75:25); Rf = 0.3 (EtOAc : Hex = 30:70); as colorless oil; Yield: 83% (99 mg); IR (KBr): 3354, 2932, 1682, 1524 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 9.70 (s, 1H), 8.78 – 8.74 (m, 2H), 8.13 (d, 1H, *J* = 8.0 Hz), 7.90 (d, 2H, *J* = 7.6 Hz), 7.55 – 7.41 (m, 6H), 6.83 (s, 1H), 6.80 (s, 2H), 4.19 (s, 4H), 3.31 – 3.24 (m, 1H), 3.03 – 2.82 (m, 4H), 1.89 – 1.67 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 200.2, 170.3, 148.1, 143.5, 142.1, 138.3, 137.0, 136.9, 136.3, 134.4, 132.9, 128.5, 128.0, 127.9, 127.4, 121.6, 121.4, 120.6, 117.3, 116.4, 116.1, 64.3, 64.3, 46.0, 41.8, 38.4, 35.7, 22.1; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{30}H_{29}N_2O_4$: 481.2127; found: 481.2111.

8-Oxo-8-phenyl-N-(quinolin-8-yl)-3-(p-tolyl)octanamide (5z) : Following the general procedure described above, **5z** was obtained after purification by column chromatography on silica gel (EtOAc:hexane = 30:70); Rf = 0.7 (EtOAc : Hex = 30:70); as colorless solid; Yield: 91% (62 mg); mp 112 – 114 ºC; IR (KBr): 3353, 2858, 1683, 1524 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 9.71 (s, 1H), 8.77 – 8.74 (m, 2H), 8.14 (d, 1H, *J* = 8.2 Hz), 7.91 (d, 2H, *J* = 7.7 Hz), 7.56 – 7.42 (m, 6H), 7.20 (d, 2H, *J* = 7.6 Hz), 7.12 (d, 2H, *J* = 7.6 Hz), 3.32 – 3.27 (m, 1H), 2.90 (t, 2H, *J* = 7.4 Hz), 2.85 (d, 2H, *J* = 7.2 Hz), 2.30 (s, 3H), 1.91 – 1.66 (m, 4H), 1.38 – 1.26 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ



200.4, 170.4, 148.0, 141.0, 138.3, 137.0, 136.3, 135.9, 134.4, 132.8, 129.3, 128.5, 128.0, 127.9, 127.4, 127.4, 121.5, 121.4, 116.4, 46.0, 42.1, 38.5, 36.0, 27.2, 24.2, 21.0; HRMS (ESI): *m/z* [M + H]$^+$ calcd for $C_{30}H_{31}N_2O_2$: 451.2386; found: 451.2371.

References

1) a) Yamaguchi, J.; Yamaguchi, A. D.; Itami, K. *Angew. Chem. Int. Ed.* **2012**, *51*, 8960. b) Feng, Y.; Chen, G. *Angew. Chem. Int. Ed.* **2010**, *49*, 958. c) Rosen, B. R.; Simke, L. R.; Thuy-Boun, P. S.; Dixon, D. D.; Yu, J. -Q.; Baran, P. S. *Angew. Chem. Int. Ed.* **2013**, *52*, 7317. d) Schçnherr, H.; Cernak, T. *Angew. Chem. Int. Ed.* **2013**, *52*, 12256.

2) a) Lyons, T. W.; Sanford, M. S. *Chem. Rev.* **2010,** *110*, 1147. b) Chen, X.; Engle, K. M.; Wang, D. -H.; Yu, J. -Q. *Angew. Chem. Int. Ed.* **2009**, *48*, 5094. c) Engle, K. M.; Mei, T. -S.; Wasa, M.; Yu, J. -Q. *Acc. Chem. Res.* **2012**, *45*, 788. d) Li, H.; Li, B. -J.; Shi, Z. -J. *Catal. Sci. Technol.*, **2011**, 1, 191. e) Peng, B.; Maulide, N. *Chem. Eur. J.* **2013**, *19*, 13274. f) Tilly, D.; Dayaker, G.; Bachu, P. *Catal. Sci. Technol.*, **2014**, *4*, 2756. g) Neufeldt, S. R.; Sanford, M. S. *Acc. Chem. Res.* **2012**, *45*, 936. h) Daugulis, O.; Roane, J.; Tran, L. D. *Acc. Chem. Res.* **2015**, *48*, 1053. i) Rouquet, G.; Chatani, N. *Angew. Chem. Int. Ed.* **2013**, *52*, 11726. j) Huang, Z.; Lim, H. N.; Mo, F.; Young, M. C.; Dong, G. *Chem. Soc. Rev.*, **2015**, *44*, 7764.

3) a) Kharasch, M. S.; Isbell, H. S. *J. Am. Chem. Soc.* **1931**, *53*, 3053. b) Murahashi, S. *J. Am. Chem. Soc.* **1955**, *77*, 6403. c) Murahashi, S.; Horiie, S. *J. Am. Chem. Soc.* **1956**, *78*, 4816. d) Kleiman, J. P.; Dubeck, M. *J. Am. Chem. Soc.* **1963**, *85*, 1544. e) Cope, A. C.; Siekman, R. W. *J. Am. Chem. Soc.* **1965**, *87*, 3272. f) Ryabov, A. D.; *Chem. Rev.* **1990**, *90*, 403. g) Moritani, I.; Fujiwara, Y. *Tetrahedron Lett.* **1967**, *8*, 1119. h) Goĺdshleger, N. F.; Tyabin, M. B.; Shilov, A. E.; Shteinman, A. A. *Zh. Fiz. Khim.* **1969**, *43*, 2174. i) Shilov, A. E.; Shul'pin, G. B. *Chem. Rev.* **1997**, *97*, 2879. j) Janowicz, A. H.; Bergman, R. G. *J. Am. Chem. Soc.* **1982**, *104*, 352. k) Hoyano, J. K.; Graham, W. A. G. *J. Am. Chem. Soc.* **1982**, *104*, 3723. l) Murai, S.; Kakiuchi, F.; Sekine, S.; Tanaka, Y.; Kamatani, A.; Sonoda, M.; Chatani, N. *Nature* **1993**, *366*, 529. m) Constable, A. G.; McDonald, W. G.; Sawkins, L. C.; Shaw, B. L. *J. Chem. Soc. Chem. Commun.* **1978**, 1061. n) Fuchita, Y.; Hiraki, K.; Uchiyama, T. *J. Chem. Soc. Dalton Trans.* **1983**, 897.

4) a) Kakiuchi, F.; Murai, S. *Acc. Chem. Res.* **2002**, *35*, 826. b) Simon, M. -O.; Martinez, R.; GenÞt, J. -P.; Darses, S. *Adv. Synth. Catal.* **2009**, *351*, 153. c) Kakiuchi, F.; Chatani, N. *Adv. Synth. Catal.* **2003**, *345*, 1077. d) Park, Y. J.; Jun, C. -H. *Bull. Korean Chem. Soc.* **2005**, *26*, 871.

5) a) Shabashov, D.; Daugulis, O. *Org. Lett.* **2005**, *7*, 3657. b) Zaitsev, V. G.; Shabashov, D.; Daugulis, O. J. Am. Chem. Soc. **2005**, *127*, 13154. c) Shabashov, D.; Daugulis, O. *J. Am. Chem. Soc.* **2010**, *132*, 3965. d) Tran, L. D.; Daugulis, O. *Angew. Chem. Int. Ed.* **2012**, *51*, 5188. e) Rodríguez, N.; Romero-Revilla, J. A.; Fernández-Ibáñez, M. A.; Carretero, J. C. *Chem. Sci.*, **2013**, *4*, 175. f) García-Rubia, A. R.; Arrayás, G.; Carretero, J. C. *Angew. Chem., Int. Ed.*, **2009**, *48*, 6511 g) García-Rubia, A. R.; Urones, B.; Arrayás, G.; Carretero, J. C. *Chem. Eur. J.*, **2010**, *16*, 9676. h) García-Rubia, A. R.; Urones, B.; Arrayás, G.; Carretero, J. C. *Angew. Chem., Int. Ed.*, **2011**, *50*, 10927. i) Chen, F. -J.; Zhao, S.; Hu, F.; Chen, K.; Zhang, Q.; Zhang, S. -Q.; Shi, B. -F. *Chem. Sci.*, **2013**, *4*, 4187. j) Zhang, Q.; Chen, K.; Rao, W.; Zhang, Y.; Chen, F. -J.; Shi, B. -F. *Angew. Chem. Int. Ed.* **2013**, *52*, 13588. k) Gu, Q.; Al Mamari, H. H.; Graczyk, K.; Diers, E.; Ackermann, L. *Angew. Chem. Int. Ed.* **2014**, *53*, 3868. l) Fan, M.; Ma, D. *Angew. Chem. Int. Ed.* **2013**, *52*, 12152.
6) a) Reddy, B. V. S.; Reddy, L. R.; Corey, E. J. *Org. Lett.*, **2006**, *8*, 3391. b) Zhang, S. -Y.; Li, Q.; He, G.; Nack, W. A.; Chen, G. *J. Am. Chem. Soc.* **2013**, *135*, 12135. C) Ano, Y.; Tobisu, M.; Chatani, N. *J. Am. Chem. Soc.* **2011**, *133*, 12984. d) Shan, G.; Yang, X.; Zong, Y.; Rao, Y. *Angew. Chem. Int. Ed.* **2013**, *52*, 13606. e) Sun, W. -W.; Cao, P.; Mei, R. -Q.; Li, Y.; Ma, Y. -L.; Wu, B. *Org. Lett.* **2014**, *16*, 480. f) Xiong, H. -Y.; Besset, T.; Cahard, D.; Pannecoucke, X. *J. Org. Chem.* **2015**, *80*, 4204.
7) a) Shabashov, D.; Daugulis, O. *J. Am. Chem. Soc.* **2010**, *132*, 3965. b) Affron, D. P.; Davis, O. A.; Bull, J. A. *Org. Lett.* **2014**, *16*, 4956. c) Wei, Y.; Tang, H.; Cong, X.; Rao, B.; Wu, C.; Zeng, X. *Org. Lett.* **2014**, *16*, 2248. d) Parella, R.; Babu, S. A. *J. Org. Chem.* **2015**, *80*, 2339. e) Parella, R.; Gopalakrishnan, B.; Babu, S. A. *Org. Lett.* **2013**, *15*, 3238. f) Parella, R.; Gopalakrishnan, B.; Babu, S. A. *J. Org. Chem.* **2013**, *78*, 11911. g) Gopalakrishnan, B.; Mohan, S.; Parella, R.; Babu, S. A. *J. Org. Chem.* **2016**, *81*, 8988. h) Reddy, C.; Bisht, N.; Parella, R.; Babu, S. A. *J. Org. Chem.* **2016**, *81*, 12143. i) Yan, S. -B.; Zhang, S.; Duan, W. -L. *Org. Lett.* **2015**, *17*, 2458. j) Hoshiya, N.; Kondo, M.; Fukuda, H.; Arisawa, M.; Uenishi, J.; Shuto, S. *J. Org. Chem.* **2017**, *82*, 2535. k) Hoshiya, N.; Kobayashi, T.; Arisawa, M.; Shuto, S. *Org. Lett.*, **2013**, *15*, 6202. l) Gou, Q.; Zhang, Z. -F.; Liu, Z. -C.; Qin, J. *J. Org. Chem.* **2015**, *80*, 3176. m) Pan, F.; Shen, P. -X.; Zhang, L. -S.; Wang, X.; Shi, Z. -J. *Org. Lett.*, **2013**, *15*, 4758. n) Tran, D. L.; Daugulis, O. *Angew. Chem. Int. Ed.* **2012**, *51*, 5188. o) Feng, Y.; Wang, Y.; Landgraf, B.; Liu, S.; Chen, G. *Org. Lett.*, **2010**, *12*, 3414.

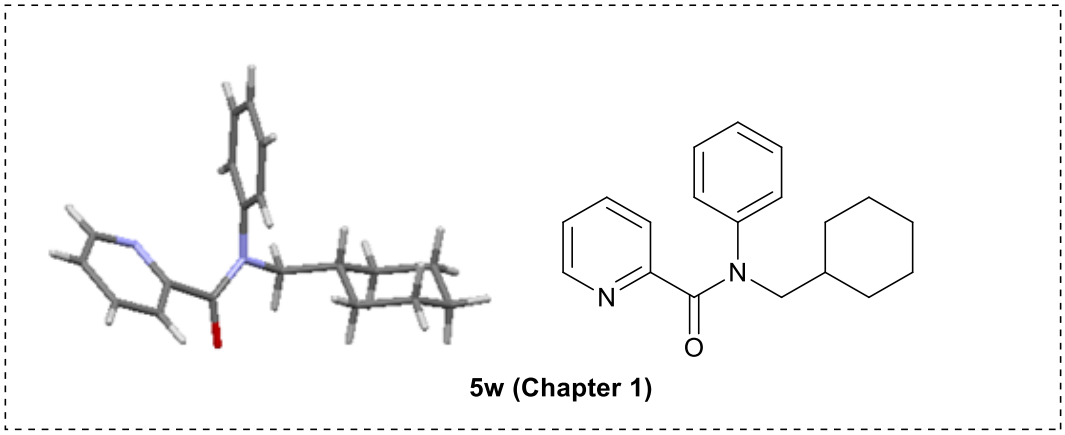
8) a) Zheng, L. -S.; Llopis, Q.; Echeverria, P. -G.; Férard, C.; Guillamot, G.; Phansavath, P.; Ratovelomanana-Vidal, V. *J. Org. Chem.* **2017**, *82*, 5607. b) Telvekar, V. N.; Patile, H. V. *Synthetic Commun.* **2011**, *41*, 131. c) Guo, Y.; Tao, G. -H.; Blumenfeld, A.; Shreeve, J. M. *Organometallics.* **2010**, *29*, 1818. d) Moriuchi, T.; Fukui, Y.; Kato, S.; Kajikawa, T.; Hirao, T. *J. Inorg. Biochem.* **2015**, *147*, 177. e) Liu, C.; Wei, W.; Yang, D.; Zheng, Y.; Bi, Y.; Chen, M.; Wang, H. *Tetrahedron*, **2015**, *71*, 6901. f) Dang, T. T.; Seayad, A. M. *Adv. Synth. Catal.* **2016**, *358*, 3373. g) Riofski, M. V.; John, J. P.; Zheng, M. M.; Kirshner, J.; Colby, D. A. *J. Org. Chem.* **2011**, *76*, 3676. h) Eshghi, H.; Hassankhani, A. *Synthetic Commun.* **2006**, *36*, 2211. i) Zhu, C.; Zhang, Y.; Zhao, H.; Huang, S.; Zhang, M.; Su, W. *Adv. Synth. Catal.* **2015**, *357*, 331. j) Savela, R.; Wärnå, J.; Murzin, D. Y.; Leino, R. *Catal. Sci. Technol.* **2015**, *5*, 2406. k) Jia, W. -G.; Zhang, H.; Li, D. -D.; Yan, L. -Q. *RSC Adv.*, **2016**, *6*, 27590. l) Wang, H.; Dai, X. -J.; Li, C. -J. *Nat. Chem.* **2017**, *9*, 374. m) Kadyrov, R.; Riermeier, T. H. *Angew. Chem. Int. Ed.* **2003**, *42*, 5472.

9) a) Stevenazzi, A.; Marchini, M.; Sandrone, G.; Vergani, B.; Lattanzio, M. *Bioorg. Med. Chem. Lett.* **2014**, *24*, 5349. b) Hänchen, A.; Rausch, S.; Landmann, B.; Toti, L.; Nusser, A.; Süssmuth, R. D. *ChemBioChem* **2013**, *14*, 625. c) Chen, K. X.; Njoroge, F. G.; Pichardo, J.; Prongay, A.; Butkiewicz, N.; Yao, N.; Madison, V.; Girijavallabhan, V. *J. Med. Chem.* **2006**, *49*, 567. d) Kast, P. *ChemBioChem.* **2011**, *12*, 2395.

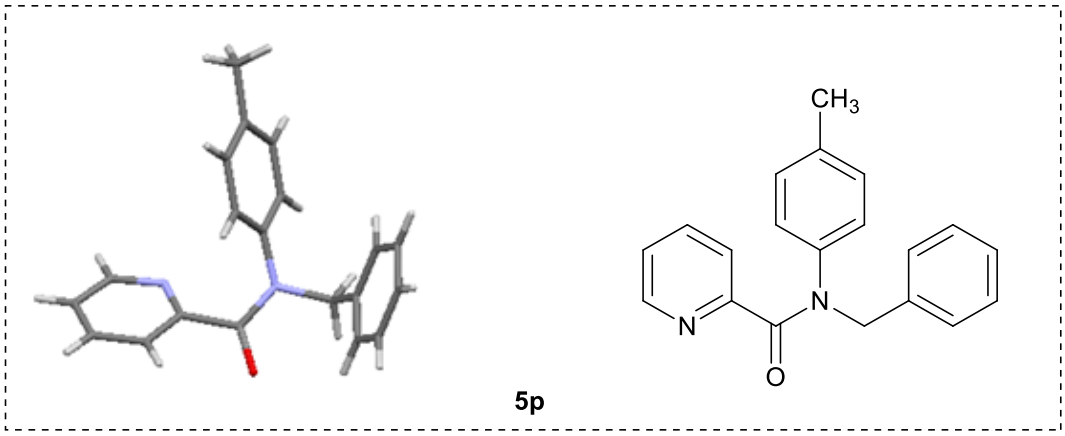
10) Chapter 28. Reductive Amination of Keto Acids. *Enzyme Catalysis in Organic Synthesis. Third Edition. Edited by Karlheinz Drauz, Harald Gröger, and Oliver May.* ©**2012** Wiley-VCH Verlag GmbH & Co. KGaA.

Appendix

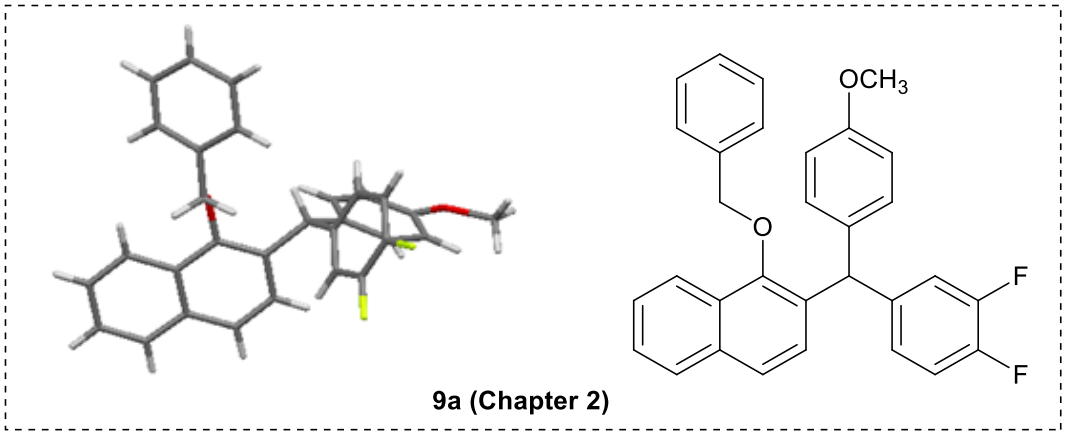
X-ray-Crystal structures



5w (Chapter 1)

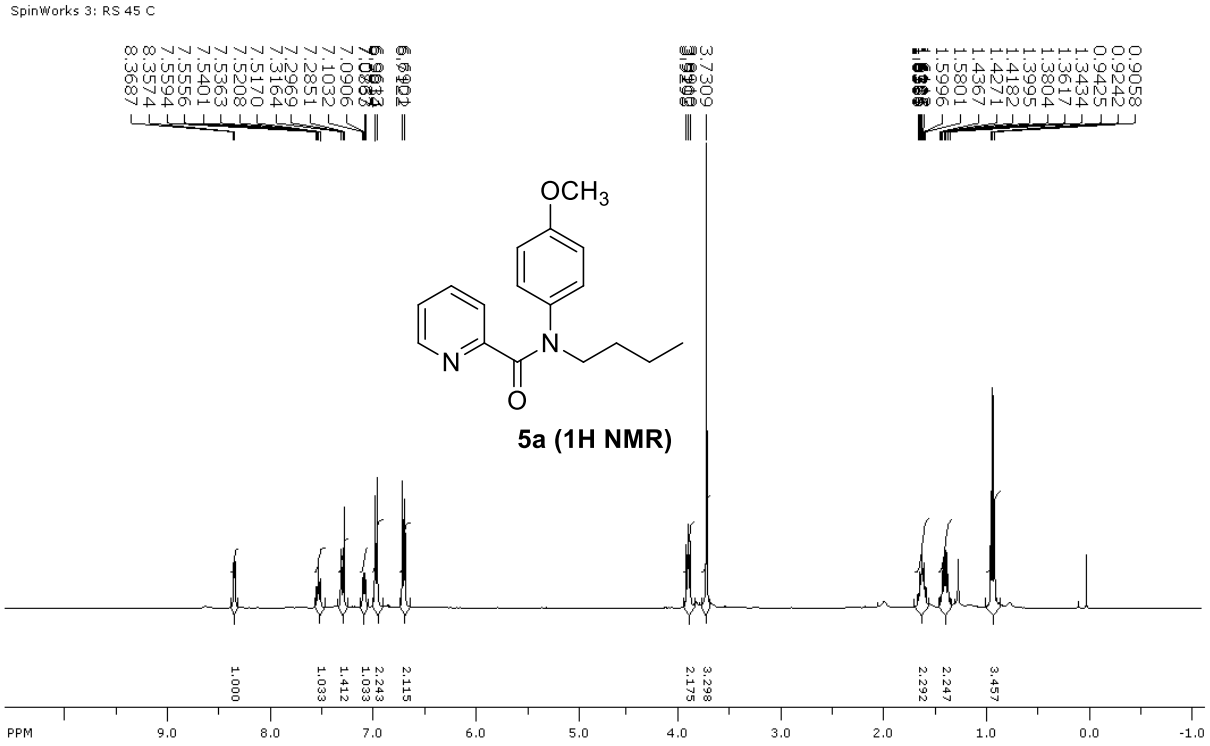


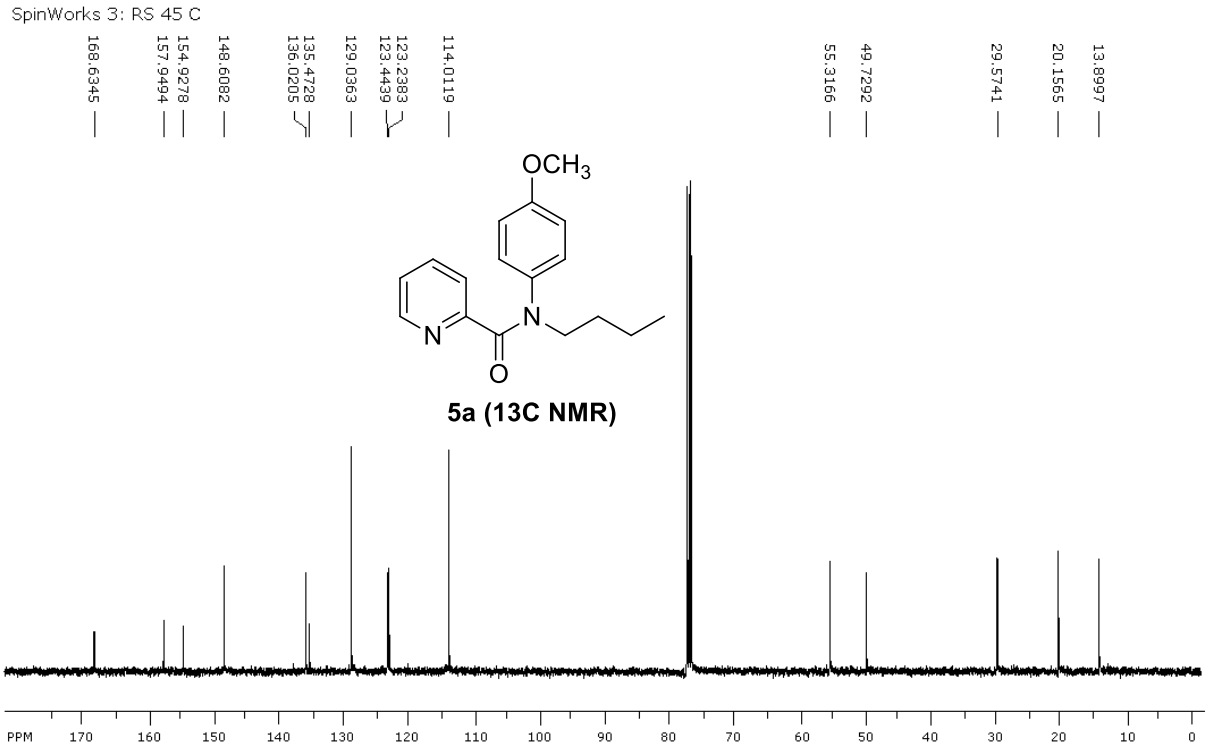
5p

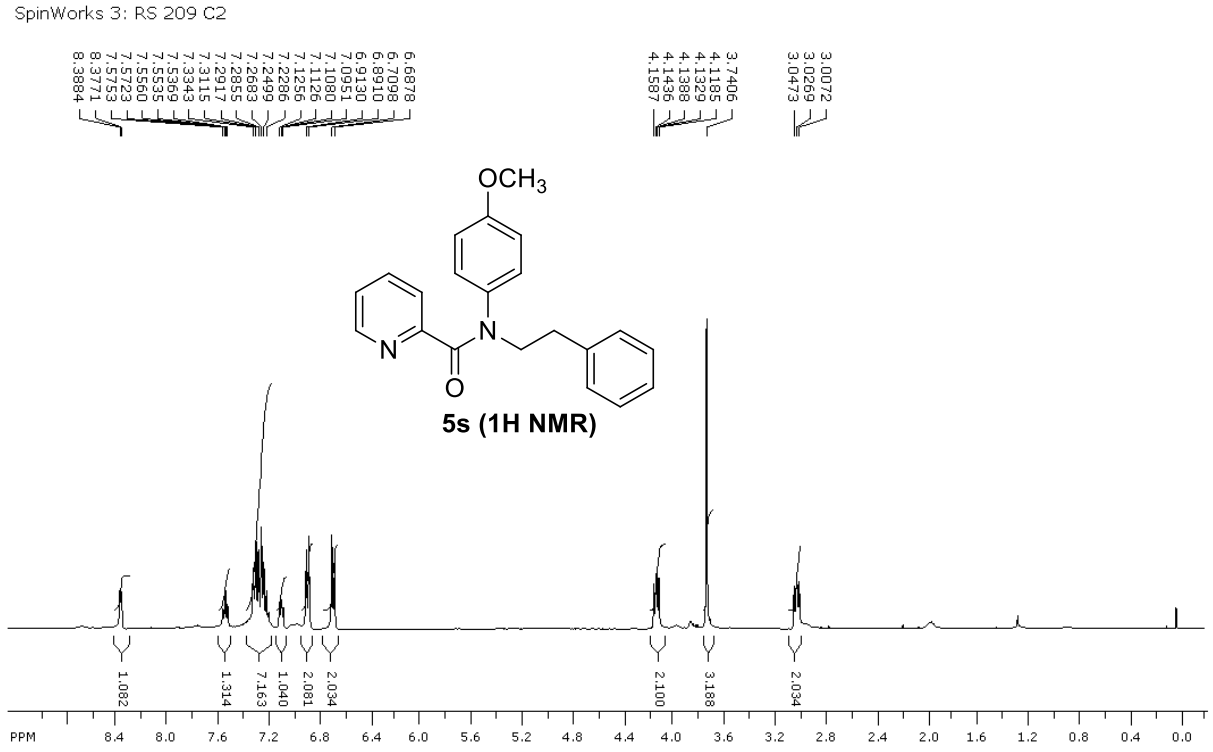


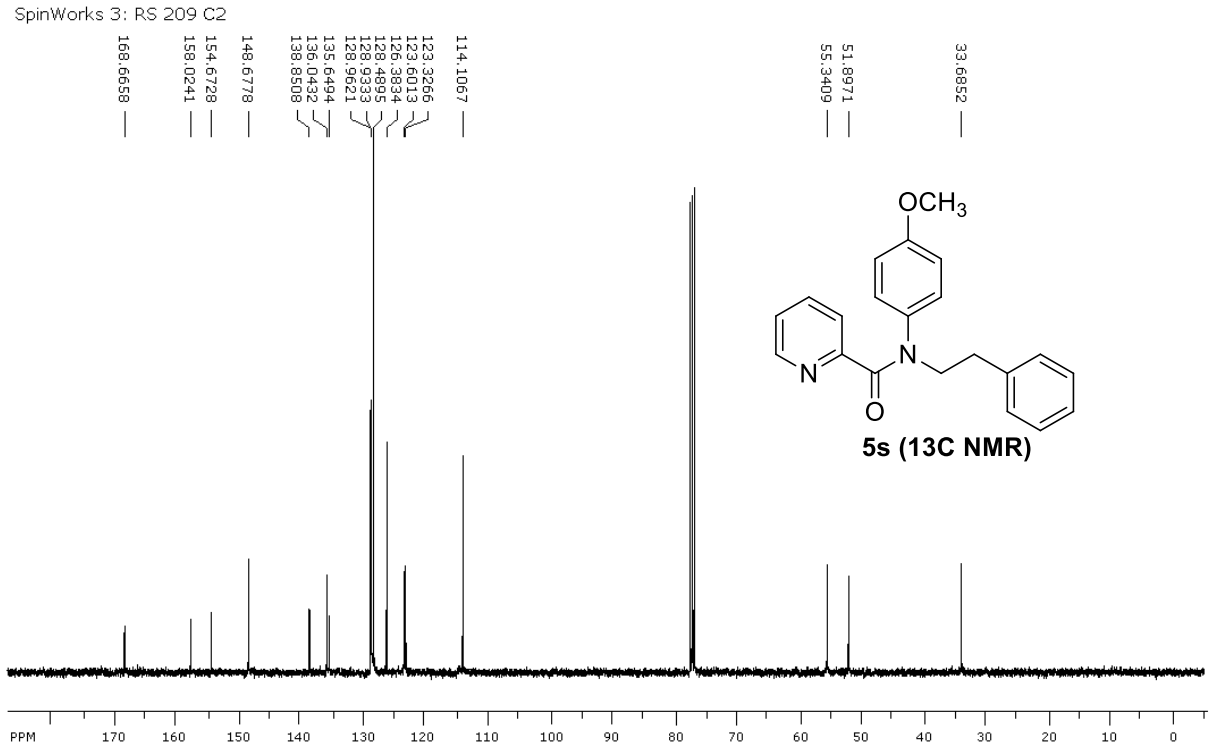
9a (Chapter 2)

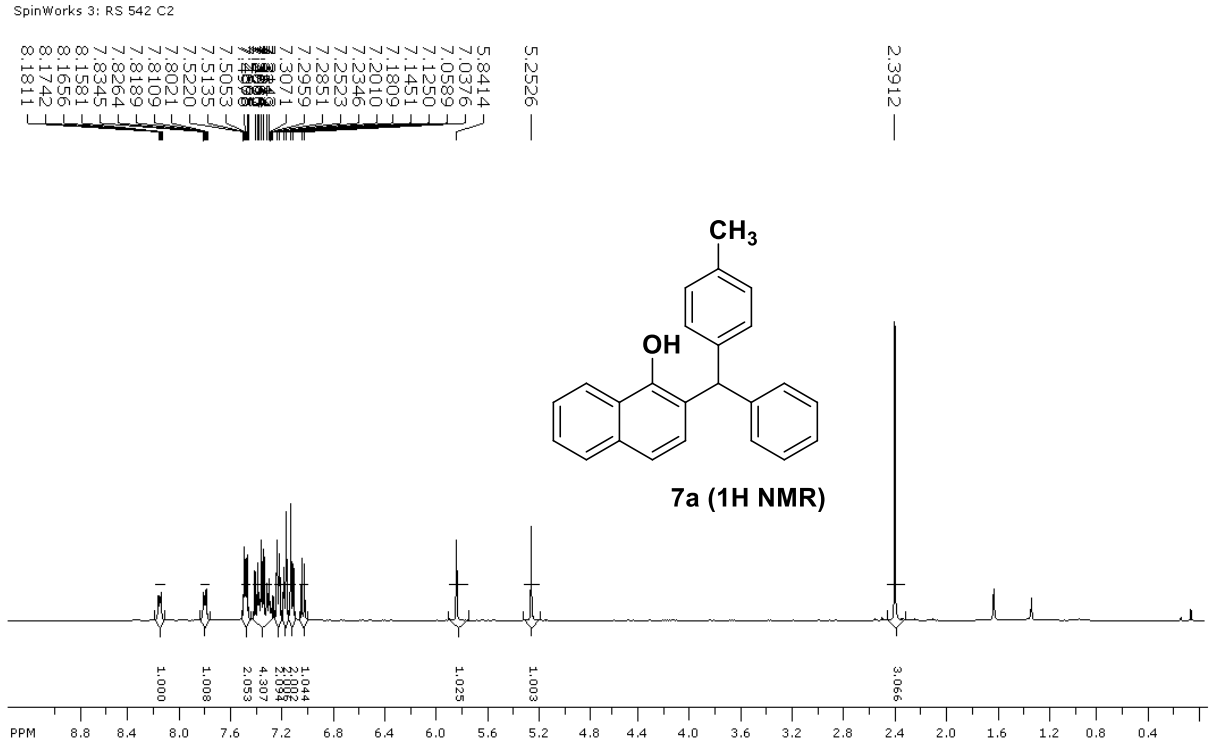
NMR Spectra Examples for Chapter 1

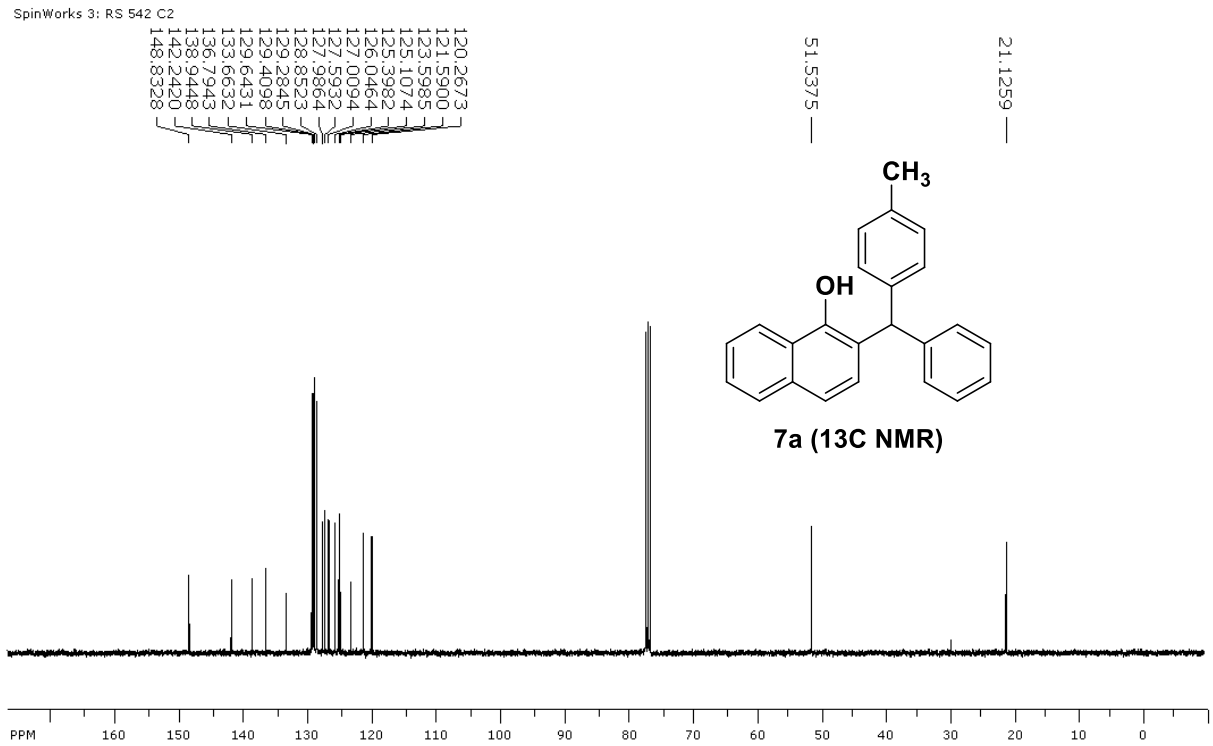


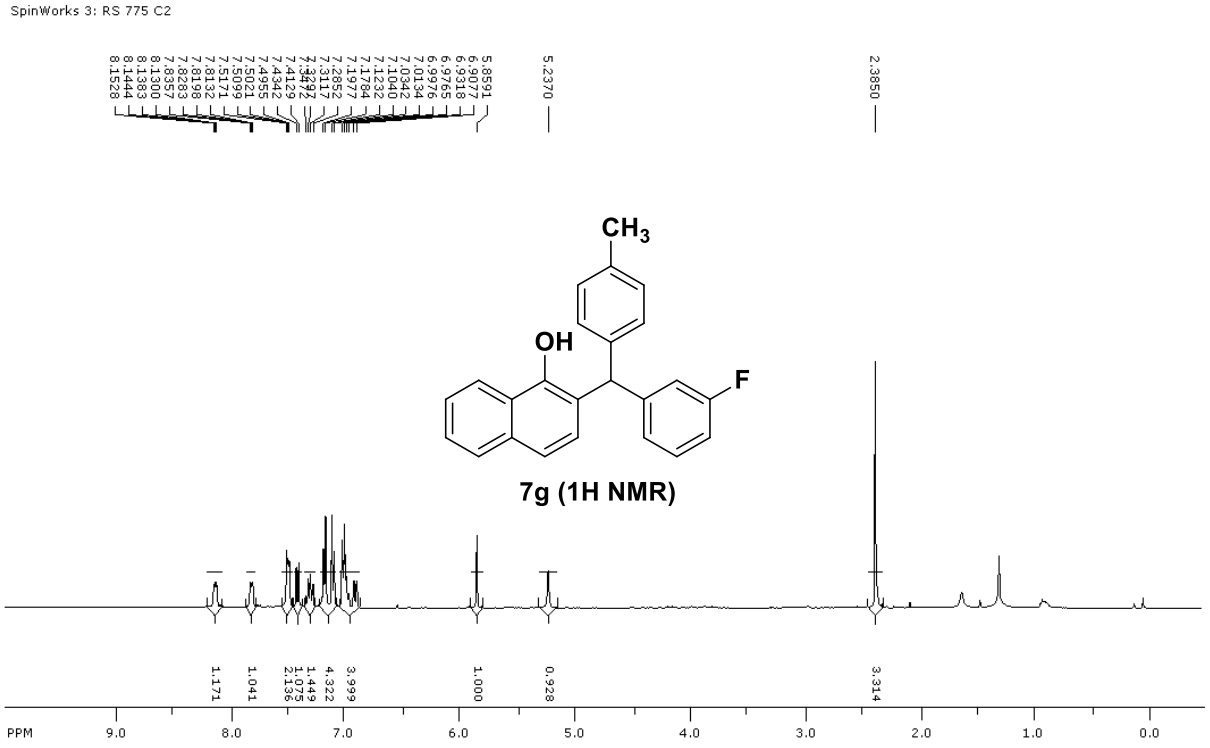


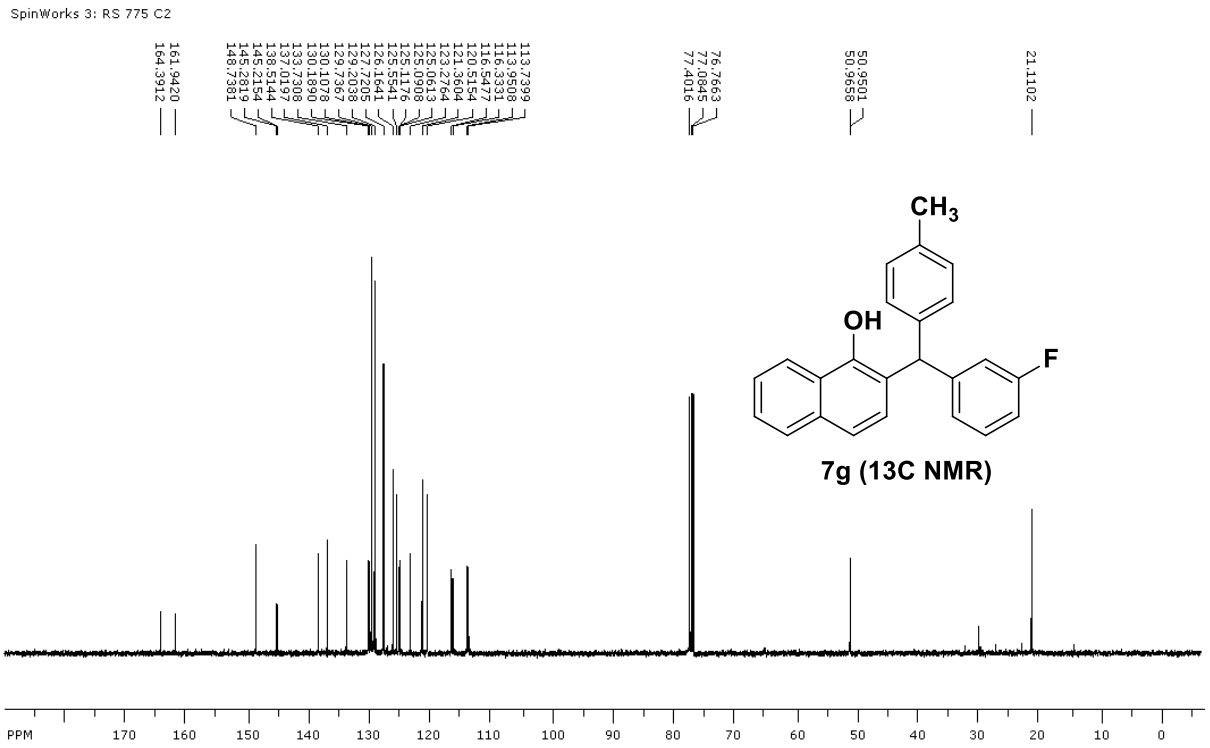

SpinWorks 3: RS 209 C2
8.3804
8.3771
7.5753
7.5723
7.5560
7.5535
7.5369
7.3343
7.3115
7.2917
7.2855
7.2683
7.2499
7.2286
7.1256
7.1126
7.1000
7.0951
6.9130
6.8910
6.7098
6.6878
4.1587
4.1436
4.1388
4.1329
4.1185
3.7406
3.0269
3.0473
3.0072
OCH3
N
N
O
5s (1H NMR)
1.082
1.314
7.163
1.040
2.081
2.034
2.100
3.188
2.034
PPM
8.4
8.0
7.6
7.2
6.8
6.4
6.0
5.6
5.2
4.8
4.4
4.0
3.6
3.2
2.8
2.4
2.0
1.6
1.2
0.8
0.4
0.0


SpinWorks 3: RS 209 C2
168.6658
158.0241
154.6728
148.6778
138.8508
136.0432
135.6494
128.9621
128.9333
128.4895
126.3834
123.6013
123.3266
114.1067
55.3409
51.8971
33.6852
OCH3
N
N
O
5s (13C NMR)
PPM
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0

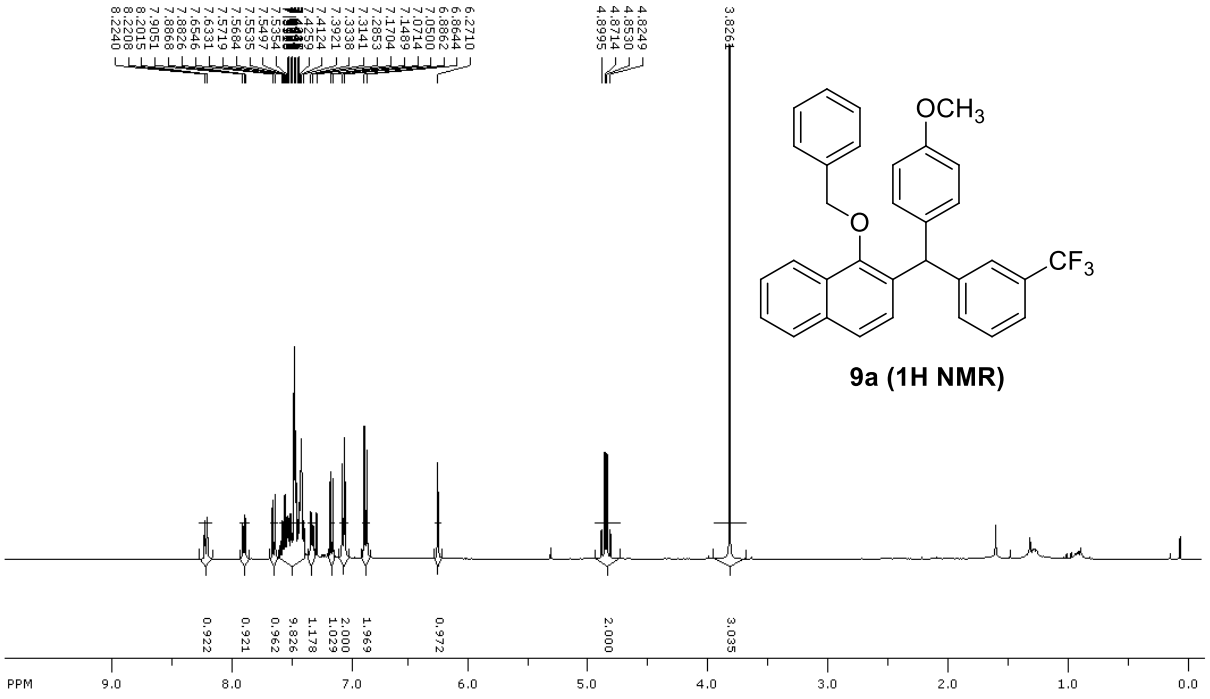

SpinWorks 3: RS 542 C2
8.1811
8.1742
8.1656
8.1581
7.8345
7.8264
7.8189
7.8109
7.8021
7.5220
7.5135
7.5053
7.3071
7.2959
7.2851
7.2523
7.2346
7.2010
7.1809
7.1451
7.1250
7.0589
7.0376
5.8414
5.2526
2.3912
CH3
OH
7a (1H NMR)
1.000
1.008
2.053
4.307
1.044
1.025
1.003
3.066
PPM
8.8
8.4
8.0
7.6
7.2
6.8
6.4
6.0
5.6
5.2
4.8
4.4
4.0
3.6
3.2
2.8
2.4
2.0
1.6
1.2
0.8
0.4


SpinWorks 3: RS 542 C2
148.8328
142.2420
138.9448
136.7943
133.6632
129.6431
129.4098
129.2845
128.8523
127.9864
127.5932
127.0094
126.0464
125.3982
125.1074
123.5985
121.5900
120.2673
51.5375
21.1259
CH3
OH
7a (13C NMR)
PPM
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0


SpinWorks 3: RS 775 C2
8.1528
8.1444
8.1383
8.1300
7.8357
7.8283
7.8198
7.8132
7.5171
7.5099
7.5021
7.4955
7.4342
7.4129
7.3492
7.3117
7.2852
7.1977
7.1784
7.1232
7.1040
7.0342
7.0134
6.9976
6.9765
6.9318
6.9077
5.8591
5.2370
2.3850
CH3
OH
F
7g (1H NMR)
1.171
1.041
2.136
1.449
1.077
4.322
3.999
1.000
0.928
3.314
PPM
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0

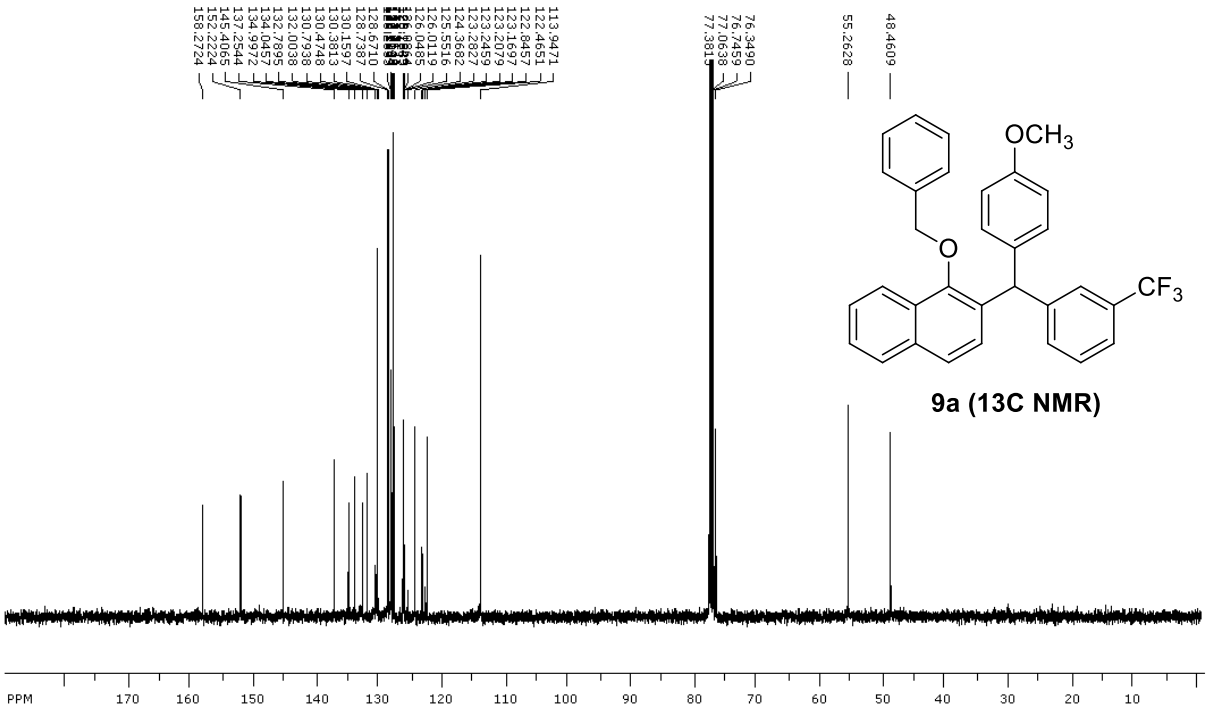

SpinWorks 3: RS 775 C2
161.9420
164.3912
148.7381
145.2819
145.2144
138.2144
137.0197
133.7308
130.1890
130.1078
129.7367
129.2038
127.7205
126.1641
125.5541
125.1176
125.0908
125.0613
123.2764
121.3604
120.5154
116.5477
116.3331
113.9508
113.7399
77.4016
77.0845
76.7663
50.9658
50.9501
21.1102
CH3
OH
F
7g (13C NMR)
PPM
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0

SpinWorks 3: rs_846_b2



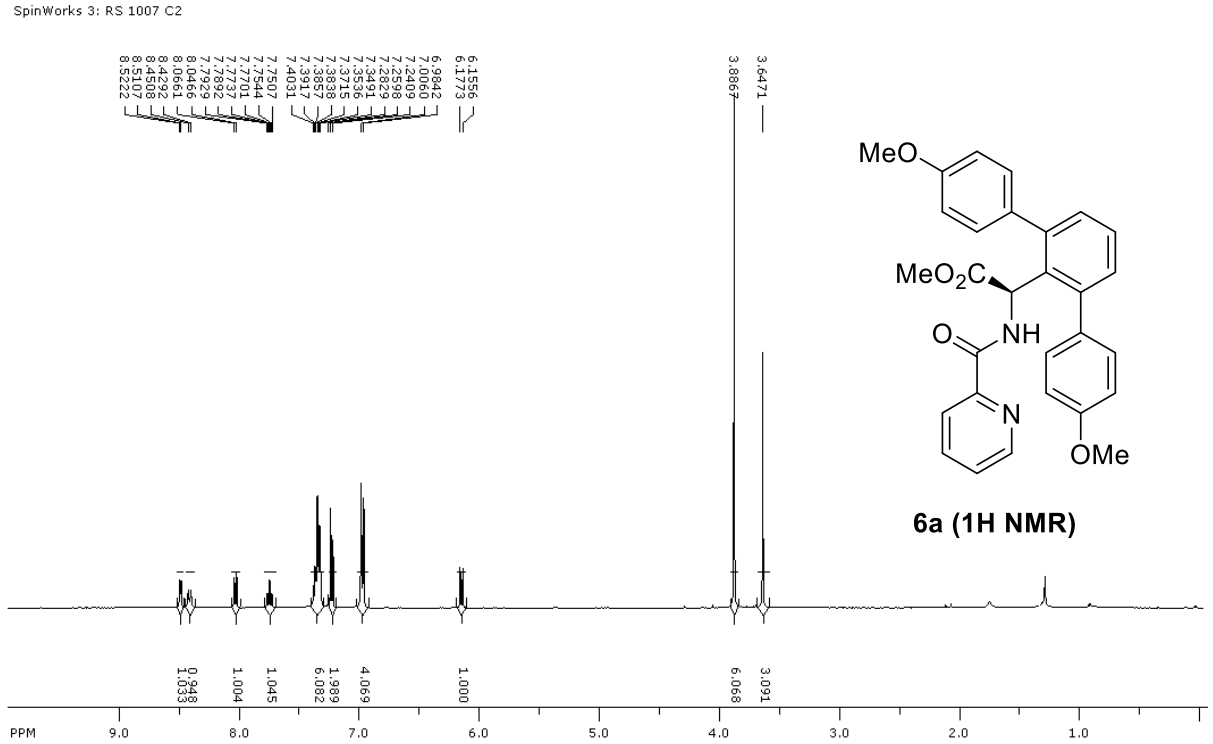
9a (1H NMR)

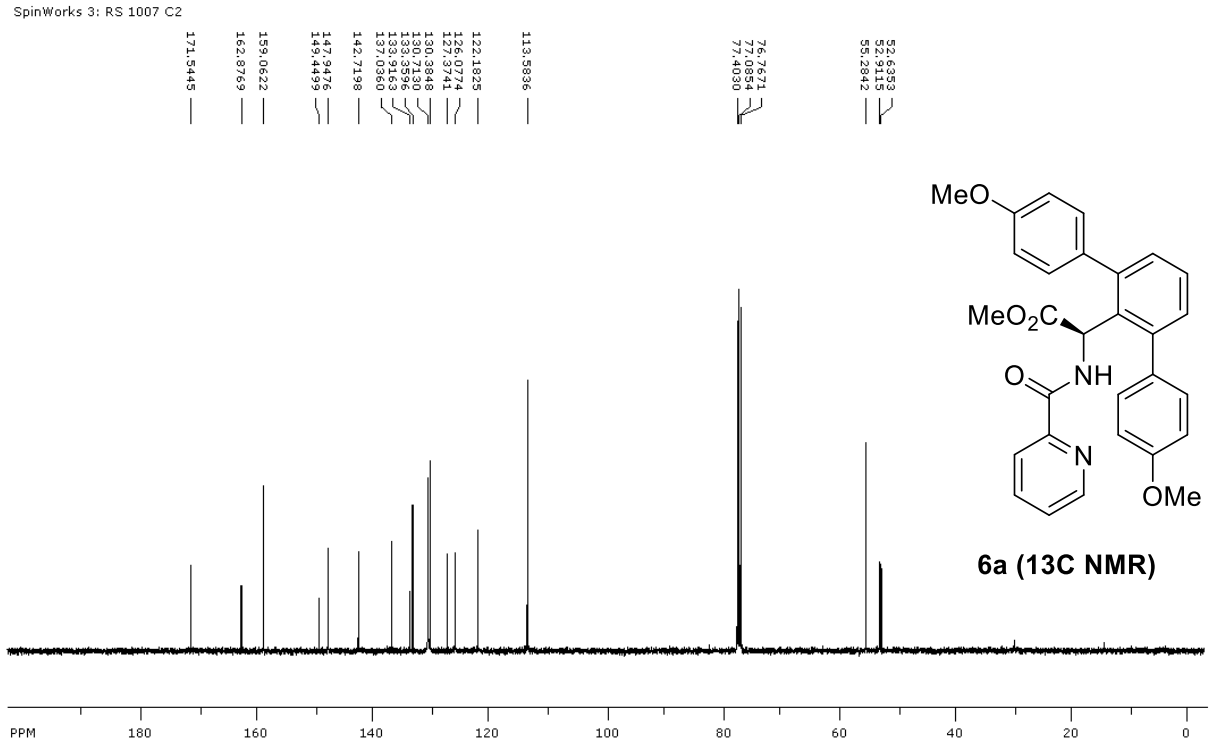
SpinWorks 3: RS 846 B2

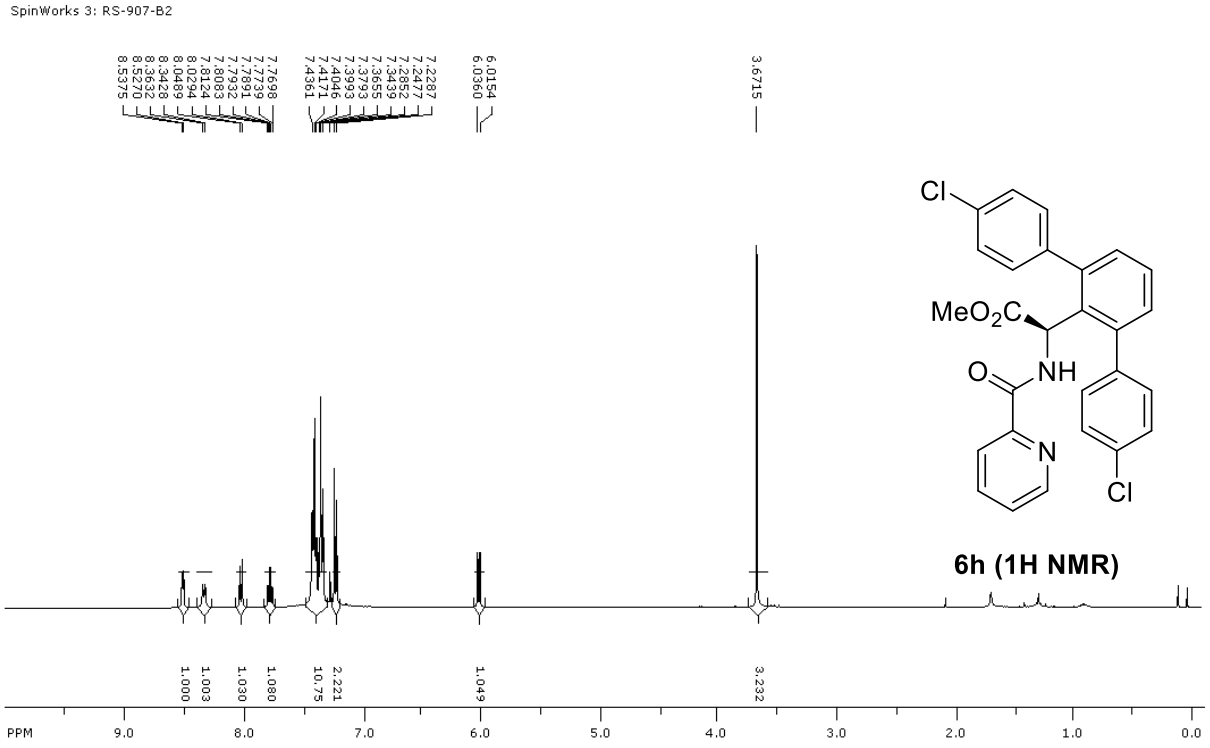


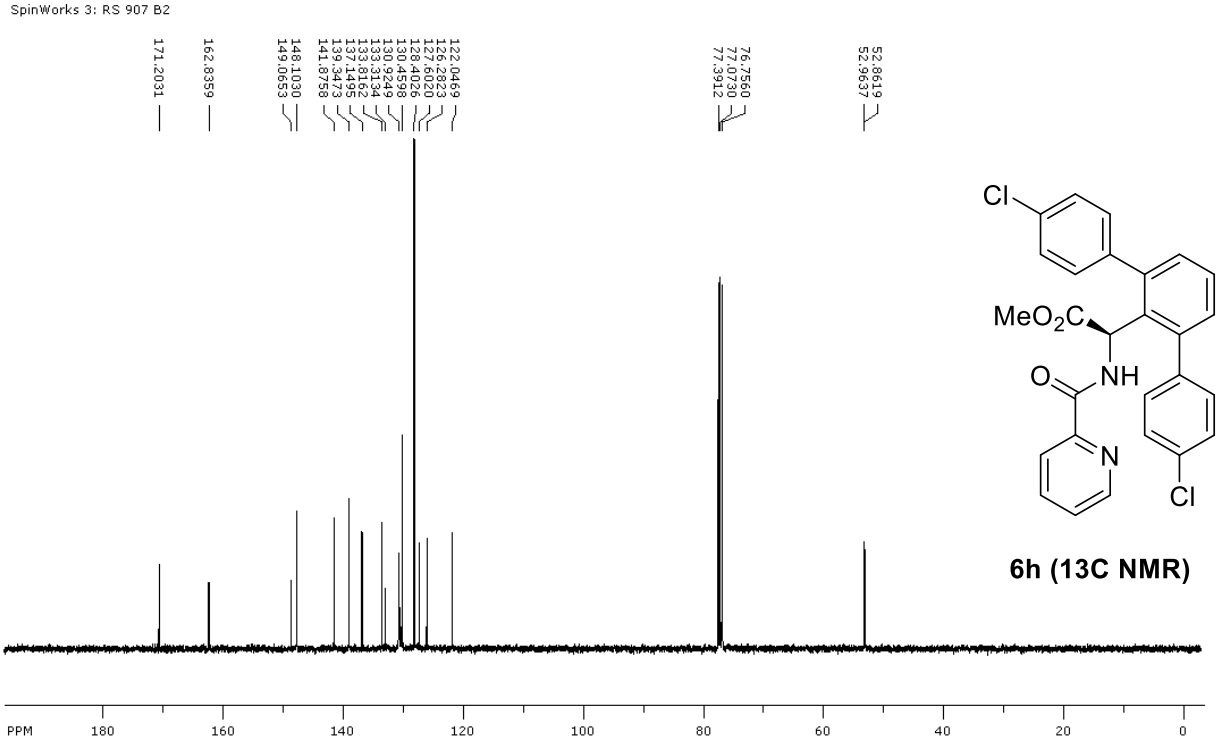
9a (13C NMR)

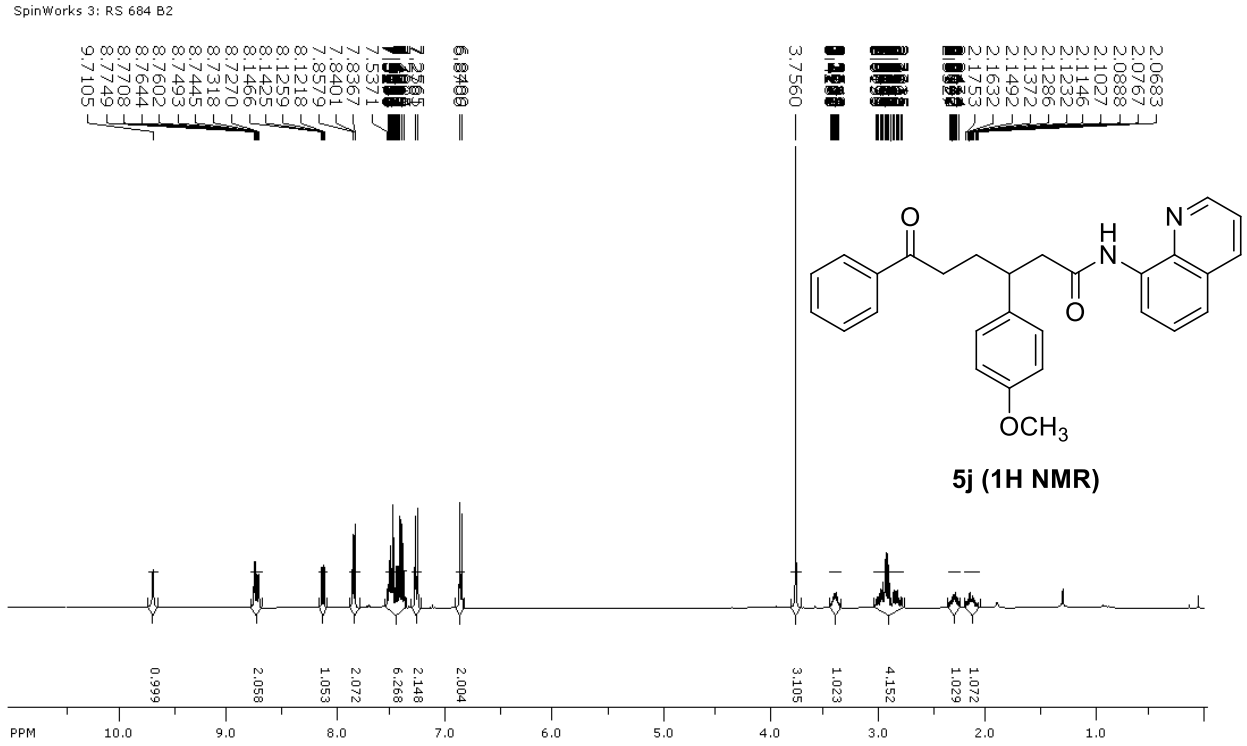
NMR Spectra Examples for Chapter 3






SpinWorks 3: RS-907-B2
8.5375
8.5270
8.3632
8.3428
8.0489
8.0294
7.8124
7.8083
7.7932
7.7891
7.7739
7.7698
7.4361
7.4171
7.4046
7.3993
7.3793
7.3655
7.3439
7.2852
7.2477
7.2287
6.0360
6.0154
3.6715
1.000
1.003
1.030
1.080
10.75
2.221
1.049
3.232
PPM
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
Cl
MeO2C
O
NH
N
Cl
6h (1H NMR)


SpinWorks 3: RS 907 B2
171.2031
162.8359
149.0653
148.1030
141.8758
139.3473
137.1495
133.8162
133.3134
130.9249
130.4598
128.4026
127.6020
126.2823
122.0469
77.3912
77.0730
76.7560
52.9637
52.8619
PPM
180
160
140
120
100
80
60
40
20
0
Cl
MeO2C
O
NH
N
Cl
6h (13C NMR)


SpinWorks 3: RS 684 B2
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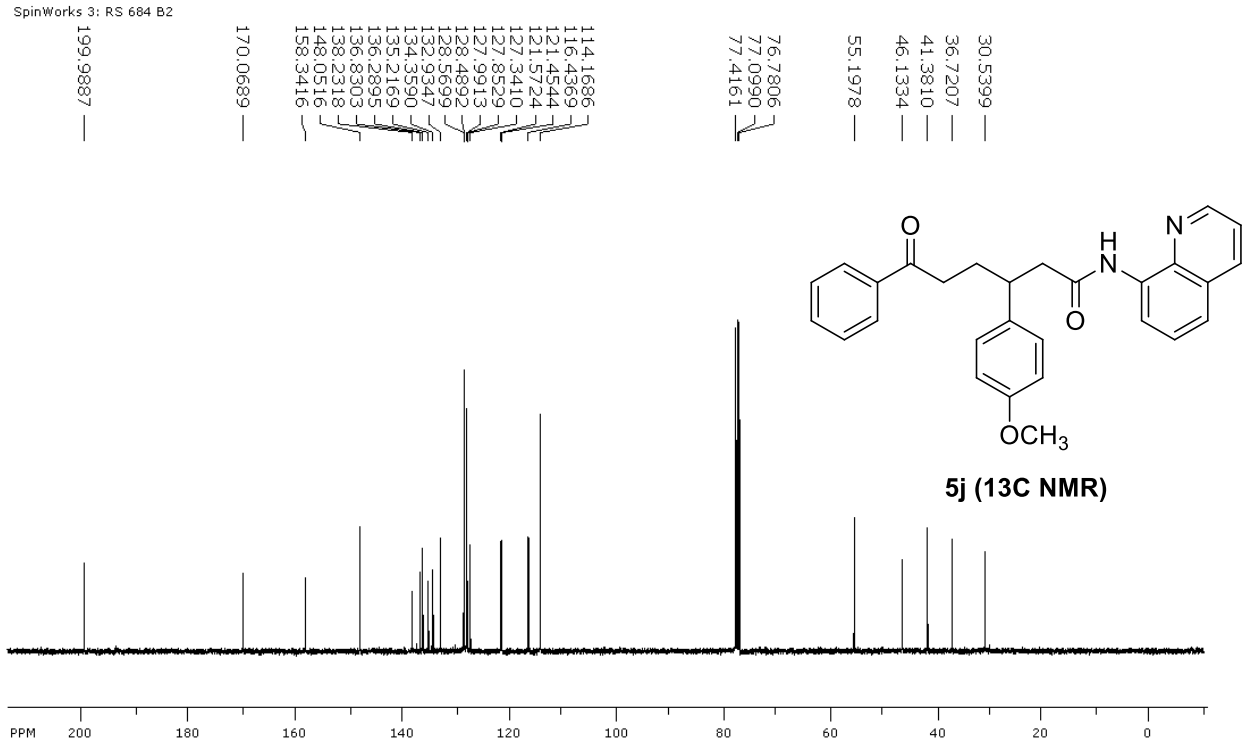
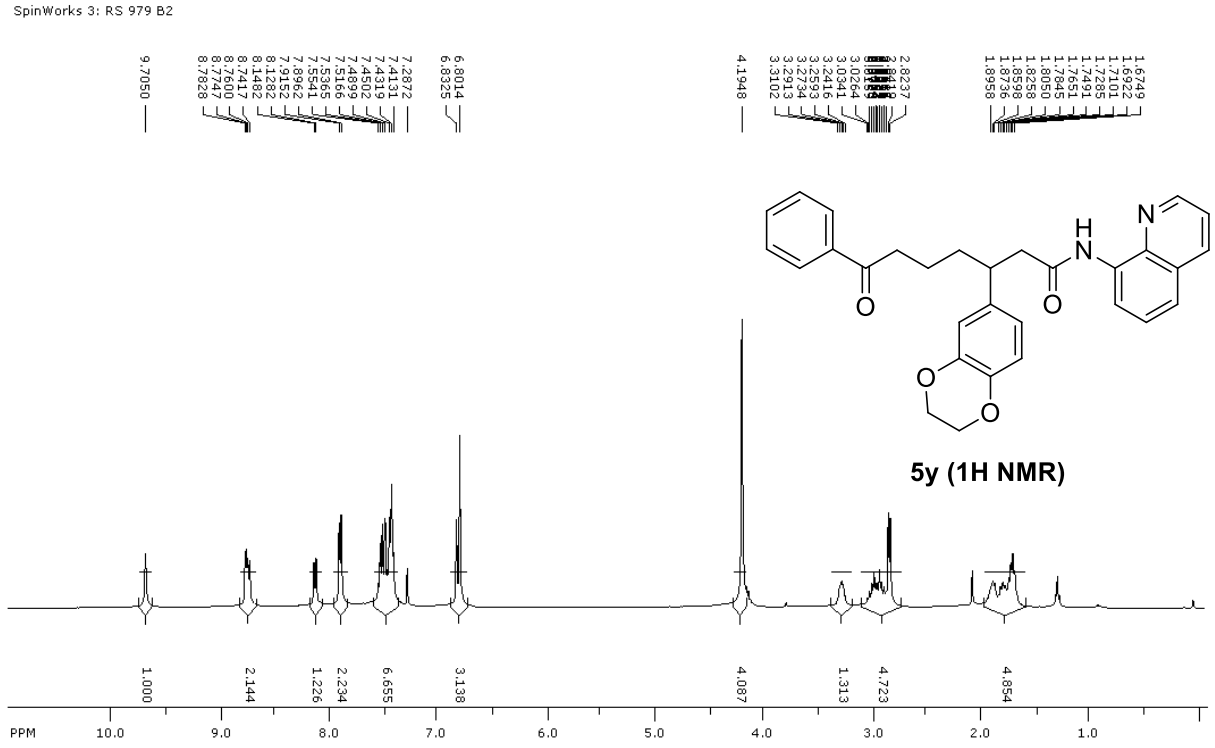
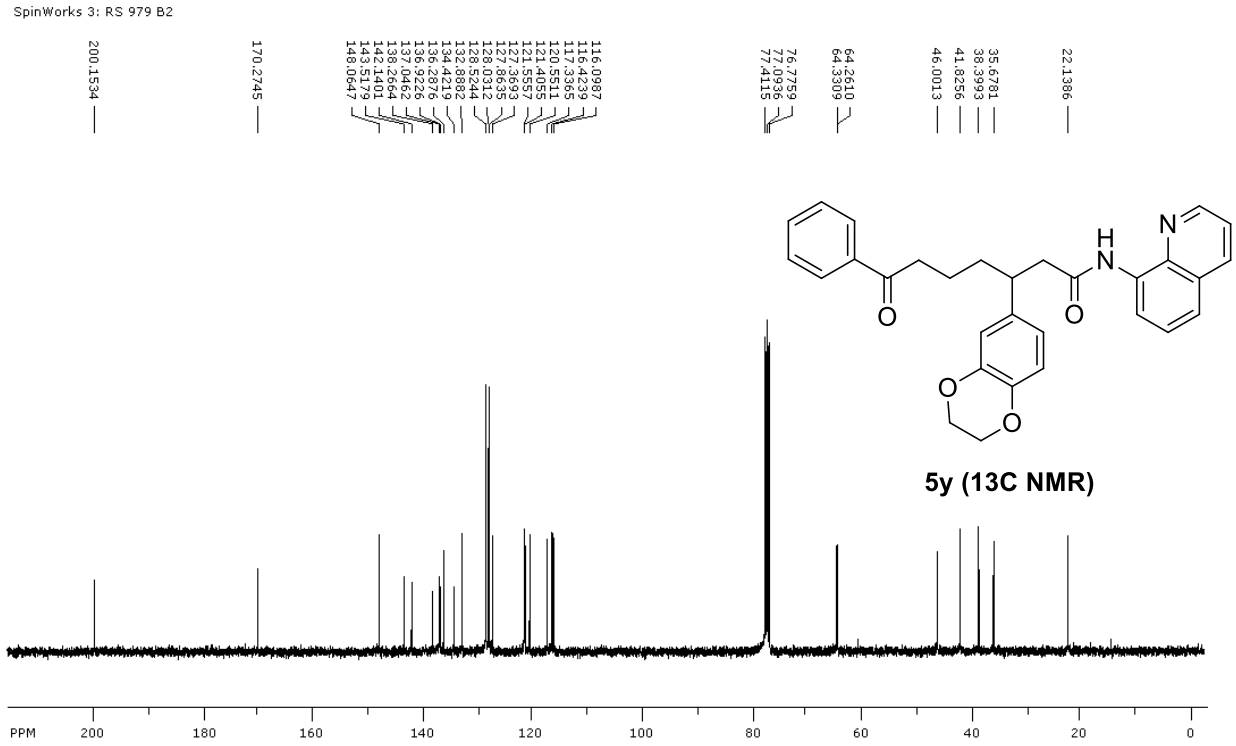
8.7749
8.7708
8.7644
8.7602
8.7493
8.7445
8.7318
8.7270
8.1466
8.1425
8.1259
8.1218
7.8579
7.8401
7.8367
7.5371
3.7560
2.0683
2.0767
2.0888
2.1027
2.1146
2.1232
2.1286
2.1372
2.1492
2.1632
2.1753
0.999
2.058
1.053
2.072
6.268
2.148
2.004
3.105
1.023
4.152
1.029
1.072
PPM
10.0
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
O
N
H
N
O
OCH3
5j (1H NMR)


SpinWorks 3: RS 684 B2
199.9887
170.0689
158.3416
148.0516
138.2318
136.8303
136.2895
135.2169
134.3590
132.9347
128.5699
128.4892
127.9913
127.8529
127.3410
121.5724
121.4544
116.4369
114.1686
77.4161
77.0990
76.7806
55.1978
46.1334
41.3810
36.7207
30.5399
PPM
200
180
160
140
120
100
80
60
40
20
0
O
N
H
N
O
OCH3
5j (13C NMR)


SpinWorks 3: RS 979 B2
9.7050
8.7828
8.7747
8.7600
8.7417
8.1482
8.1282
7.9152
7.8962
7.5541
7.5365
7.5166
7.4899
7.4502
7.4319
7.4131
7.2872
6.8325
6.8014
4.1948
3.3102
3.2913
3.2734
3.2593
3.2416
3.0341
3.0264
2.8237
1.8958
1.8736
1.8598
1.8258
1.8050
1.7845
1.7651
1.7491
1.7285
1.7101
1.6922
1.6749
H
N
O
O
O
O
N
5y (1H NMR)
1.000
2.144
1.226
2.234
6.655
3.138
4.087
1.313
4.723
4.854
PPM
10.0
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0


SpinWorks 3: RS 979 B2
200.1534
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148.0647
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142.1401
138.2664
137.0462
136.9226
136.2876
134.4219
132.8882
128.5244
128.0312
127.8635
127.3693
121.4557
121.3051
120.5511
117.3365
116.4939
116.0987
77.4115
77.0916
76.7759
64.3909
64.2610
46.0013
41.8256
38.3993
35.6781
22.1386
H
N
O
O
O
O
N
5y (13C NMR)
PPM
200
180
160
140
120
100
80
60
40
20
0