Study of Copper(I)-Catalyzed *C-C*, *C-N* and *C-O* Bonds Formation, and Palladium(II)-Catalyzed One-pot Conversion of Aldehydes to Primary Amides

A Thesis Submitted
in Partial Fulfillment of the Requirements
for the Degree of

DOCTOR OF PHILOSOPHY

by

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July 2012

Dedicated to

My

Family Members

INDIAN INSTITUTE OF TECHNOLOGY GUWAHATI

Department of Chemistry

STATEMENT

I hereby declare that the matter embodied in this thesis is the result of investigations carried out by me in the Department of Chemistry, Indian Institute of Technology Guwahati, Guwahati, India under the supervision of Prof. Tharmalingam Punniyamurthy.

In keeping with the general practice of reporting scientific observations, due acknowledgement has been made wherever the work described is based on the findings of other investigators.

Guwahati — Md Ashif Ali

July 2012

INDIAN INSTITUTE OF TECHNOLOGY GUWAHATI

Department of Chemistry

CERTIFICATE

This is to certify that Mr. Md Ashif Ali has been working under my supervision since July 2009. I am forwarding his thesis entitled "*Study of Copper(I)-Catalyzed C-C, C-N and C-O Bonds Formation, and Palladium(II)-Catalyzed One-pot Conversion of Aldehydes to Primary Amides*" being submitted for the Ph.D. degree of this institute. I certify that he has fulfilled all the requirements according to the rules of this institute, and regarding the investigations embodied in his thesis and this work has not been submitted elsewhere for a degree.

Guwahati

July 2012

Prof. Tharmalingam Punniyamurthy

Supervisor

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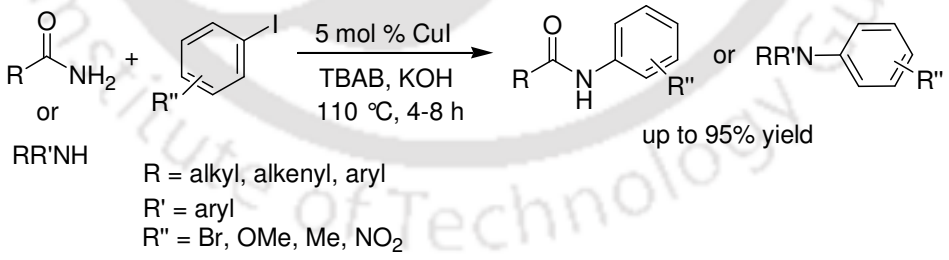
Md Ashif Ali

Abstract

The thesis has four chapters. The first three chapters describe the *N*-arylation of amides and imidazoles with aryl iodides, synthesis of substituted 2-arylbenzoxazoles and polysubstituted indoles via copper(I)-catalyzed *C-N*, domino *C-N*/*C-O* and *C-C* bonds formation, respectively. The fourth chapter contains the palladium(II)-catalyzed one pot conversion of aldehydes to amides.

1. CuI-Catalyzed *N*-Arylation of Amides and Imidazoles with Aryl Iodides

The transition-metal catalyzed carbon-nitrogen bond formation via cross-coupling reaction is a powerful tool for the synthesis of numerous important compounds in biological, material and pharmaceutical sciences. *N*-Arylations of amides and imidazoles are of particular interest because the products contain structural motifs of numerous natural products and biologically active molecules. This chapter describes *N*-arylation of amides and azoles with aryl iodides using CuI as a catalyst in TBAB under ligand free condition (Scheme 1). The reactions are efficient affording the cross-coupled products in short time in high yields.

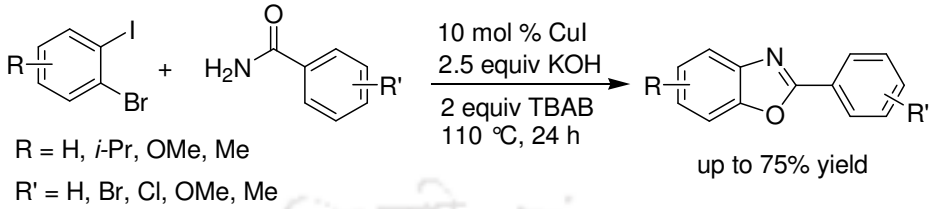


Scheme 1

2. Domino CuI-Catalyzed Synthesis of 2-Arylbenzoxazoles

Benzoxazole moieties are an important class of heterocycles present in various natural products and biologically active compounds. In this chapter, we report the synthesis of 2-arylbenzoxazoles from 2-bromoiodobenzenes and primary amides via CuI-catalyzed

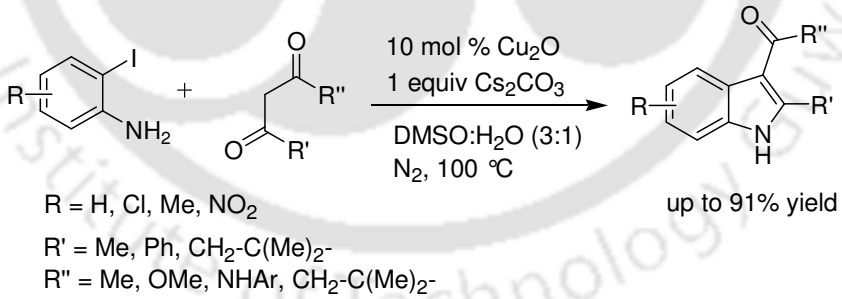
domino *C-N/C-O* bond formation in tetrabutylammonium bromide (TBAB) at 110 ˚C (Scheme 2). The reaction is simple, general and free from addition of organic solvents. Further, the reactions are regiospecific providing one regioisomer exclusively.



Scheme 2

3. Domino Cu_2O-Catalyzed Synthesis of Polysubstituted Indoles

Indoles are probably the most common heterocycles found in nature with immense medicinal importance. Indoles are also important structural constituent for the development of agrochemicals, materials and perfumes. This chapter focuses on the synthesis of polysubstituted indoles by Cu_2O-catalyzed domino reaction of 2-haloanilines with a series of 1,3-dicarbonyl compounds, such as 1,3-diketone, *β*-keto ester and *β*-keto amide, in a 3:1 mixture of DMSO–water at 100 ˚C (Scheme 3). The protocol is simple, general and atom economical for the regiospecific synthesis of polysubstituted indoles in high yields.

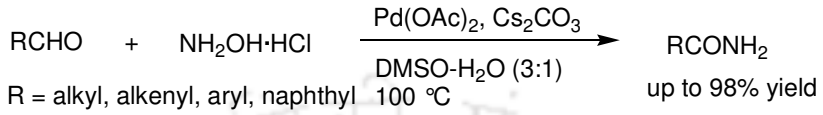


Scheme 3

4. Pd(II)-Catalyzed One-pot Conversion of Aldehydes to Amides

Synthesis of primary amides is one of the most important processes because of their utilities in a wide range of applications in academia and industry, especially as intermediates in organic synthesis, raw material for plastics, detergents, lubricants and

pharmaceuticals. This chapter describes the one-pot transformation of aldehydes with hydroxylamine hydrochloride to primary amides using $Pd(OAc)_2$ as a catalyst in aqueous DMSO at 100 ˚C (Scheme 4). This method is efficient for conversion of aryl, alkyl and alkenyl aldehydes into primary amides.



Scheme 4

Contents

Chapter I

CuI-Catalyzed *N*-Arylation of Amides and Imidazoles with Aryl Iodides

The carbon-nitrogen bond formation *via* cross-coupling reaction is a powerful tool for the synthesis of numerous important compounds, that are of biological, material and pharmaceutical interest.[1] *N*-Arylations of amides and imidazoles are of particular interest because the products have structural motifs of numerous natural products and biologically active molecules (Figure 1).[2] The common classical synthetic methods used for their preparation are well known Ullmann and Goldberg type coupling reactions, however, they require high temperature (>200 °C) along with hazardous organic solvents such as pyridine, collidine, nitrobenzene and stoichiometric or greater amount of copper reagents that on scale-up leads to the problem of waste disposal.[3] To overcome these drawbacks transition-metal catalyzed *C-N* cross-coupling methods have been developed in recent years. For examples, palladium[4] catalysts along with bulky phosphorus ligand such as P(*t*-Bu)$_3$,[4a] biarylmonophosphine,[4c,4g,4m] xantphos,[4b,4f,4h] ferrocenyl phosphine,[4i,4j] and copper[5,6] catalysts with diamine,[5b-c,5h-i] 1,3-dicarbonyl,[6s] amino acids,[5d,6a] 1,10-phenanthroline,[6e] 8-hydroxyquinoline,[6h] oxime[5e,6t] and enaminones[6q] ligands have been reported for the *N*-arylation of amides and imidazoles with aryl halides. Although these developments have been done for *N*-arylation of amides and imidazoles with aryl iodides but still easier, more efficient, environmentally benign and cost effective methods are to be developed.

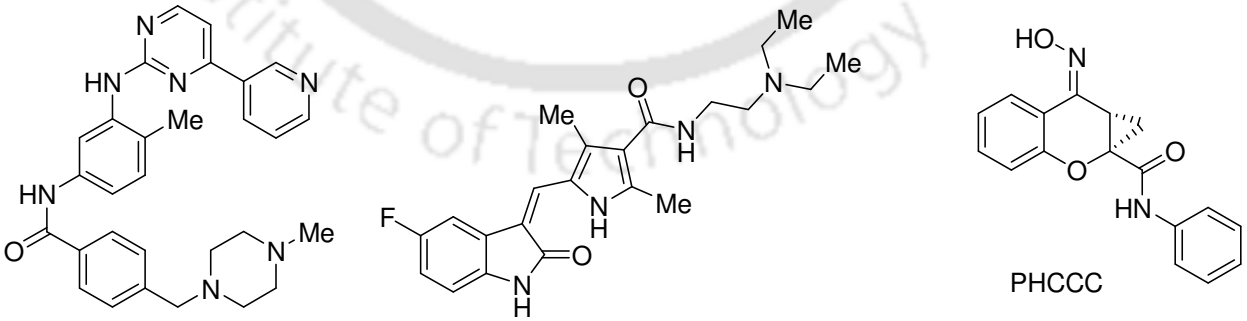
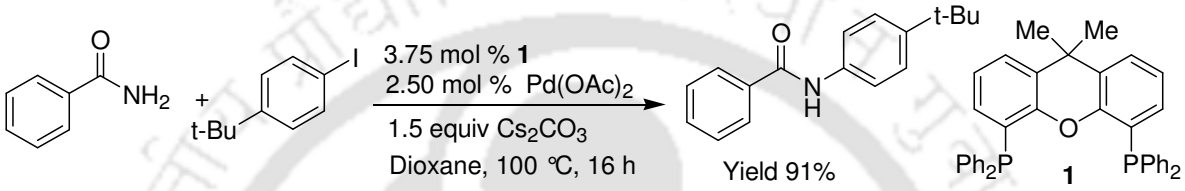


Figure 1 Examples of Some Biologically Active Molecules

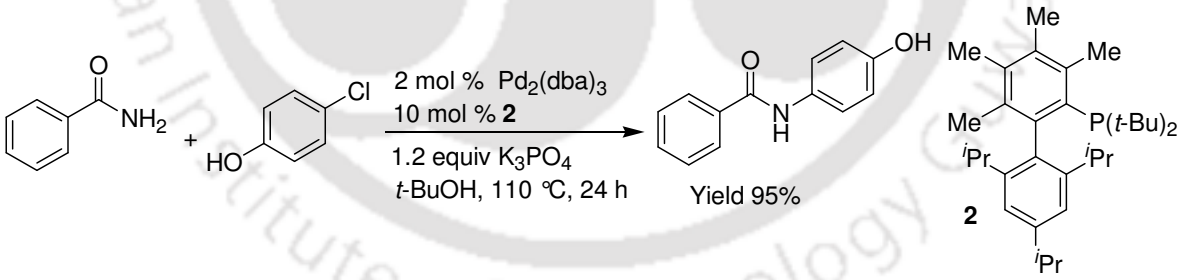
1.1 Palladium Catalysts

The palladium catalysts with suitable bulky phosphorous ligands have been studied for the *N*-arylation of amides. First direct *N*-arylation of amides, carbamates and sulfonamides with aryl iodides, -bromides, -chlorides and -triflates in the presence of $Pd(OAc)_2$ and xantphos **1** was discovered by Buchwald and co-workers (Scheme 1).[4f] The reaction works well in THF as well as in 1,4-dioxane with Cs_2CO_3 base at 45-110 °C to give the desired *N*-arylated products in 66-99% yield.



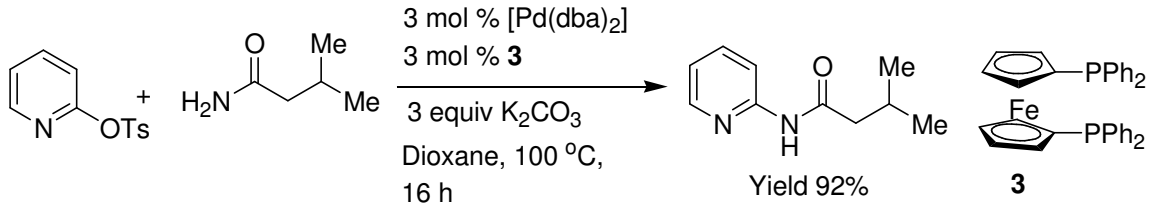
Scheme 1

The same group has reported the amidation of less reactive aryl chloride with aromatic or aliphatic amides and sulphonamides in the presence of $Pd_2(dba)_3$ and bulkier monodentate biarylphosphine ligand **2** (Scheme 2).[4d] The reaction works smoothly with K_3PO_4 in *t*-BuOH providing the desired *N*-arylated amides in good yield.



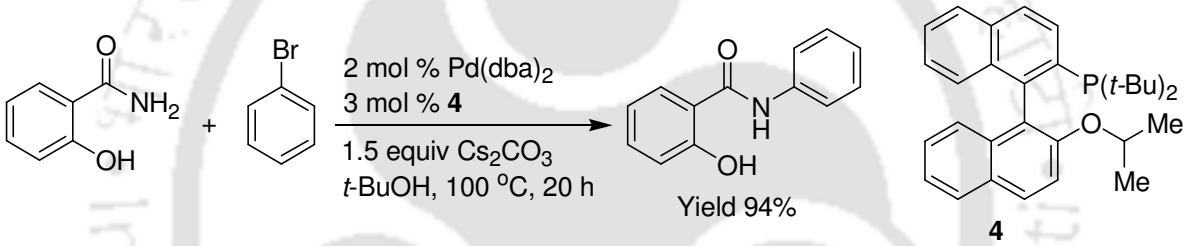
Scheme 2

Skrydstrup and co-workers have described a protocol for *N*-arylation of amides with heteroaromatic tosylates such as pyridine, pyrimidine, quinoline and quinoxaline using the combination of [$Pd(dba)_2$] and DPPF, 1,1'-bis(diphenylphosphino)ferrocene **3** along with K_2CO_3 in dioxane at 100 °C (Scheme 3).[4m] The reaction is also effectively used for the *N*-arylation of oxazolidinones, lactams, anilines and indoles.



Scheme 3

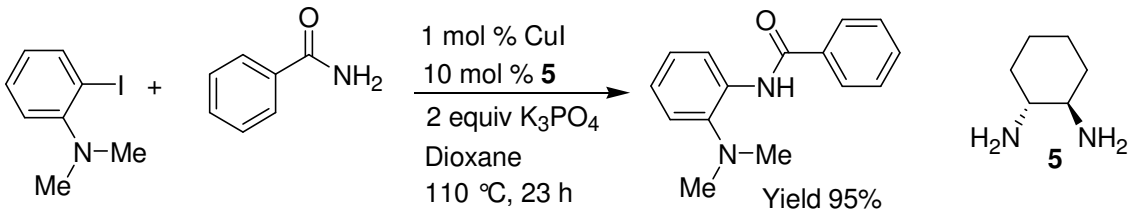
Recently, Zhang and co-workers have reported palladium catalyzed intermolecular amidation between aryl halides and amides by using 2-dialkylphosphino-2′-alkoxyl-1,1′-binaphthyl **4** which is both bulky and electron-rich.[4o] A variety of amides, including aliphatic and aromatic primary amides, lactams, and carbamates, were found to be good substrates for the amidation and exhibited good functional group compatibility (Scheme 4).



Scheme 4

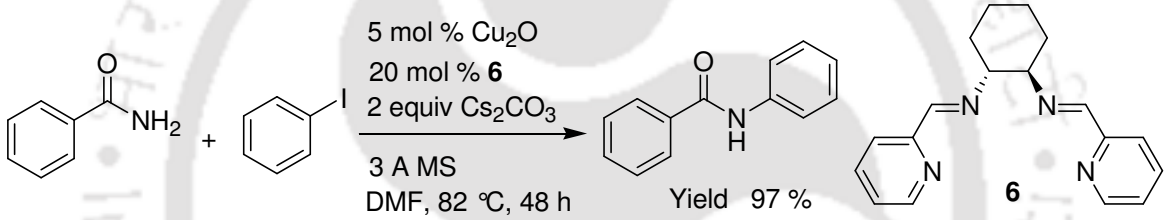
1.2 Copper Catalysts

The use of copper catalysts instead of air sensitive palladium catalysts is more advantageous because the copper salts are considerably cheaper, readily available and more stable compared to palladium salts. Buchwald and co-workers have studied *N*-arylation of amides and a wide range of nitrogen containing heterocycles by using readily available air stable CuI and racemic *trans*-1,2-cyclohexanediamine **5**.[5h] The reaction conditions involve the use of 1-10 mol % of CuI, 10 mol % ligand **5** and K_3PO_4, Cs_2CO_3 or K_2CO_3 as base in dioxane at 110 °C (Scheme 5).



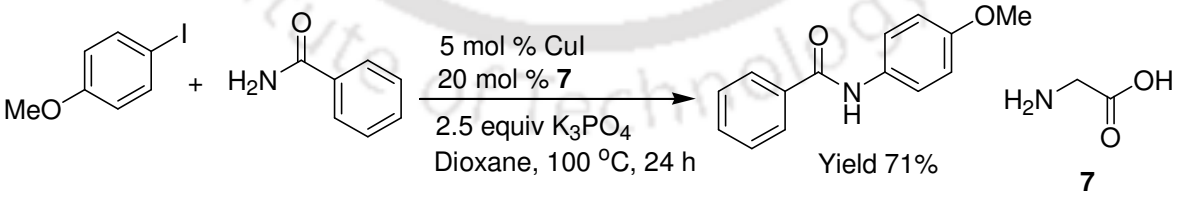
Scheme 5

Marc Taillefer groups have used Cu_2O as catalyst for *N*-arylation of amides and imidazoles in the presence of Schiff base **6**, Cs_2CO_3 and molecular sieves in DMF at 82 ºC.[5e] A variety of substituted aryl bromides and iodides were readily coupled with a number of amides and azoles to provide desired *N*-arylated amides and azoles in good yield (Scheme 6).



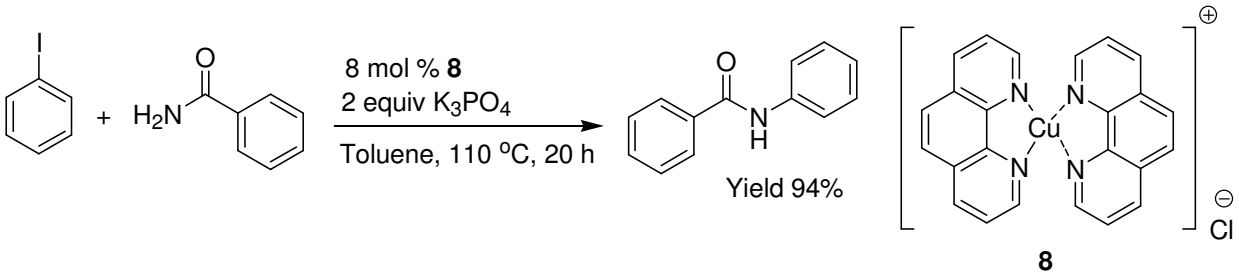
Scheme 6

Guo and co-workers have developed CuI/amino acid catalyst for *N*-arylation of amides with aryl halides.[6a] They have found that the yield of amidated products is dependent on base used in the reaction and that the best conditions are CuI and glycine **7** with K_3PO_4 base in dioxane at 100 °C (Scheme 7).



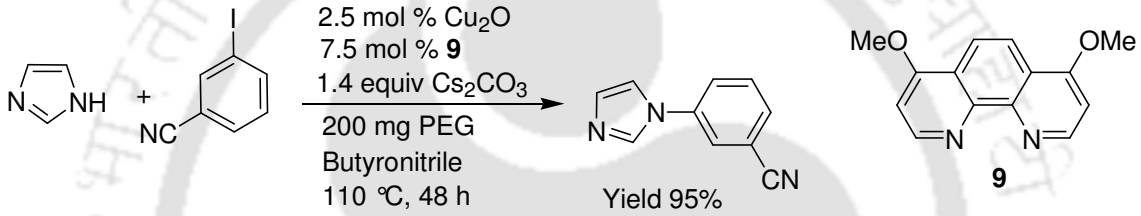
Scheme 7

Moriwaki and co-workers have used copper(I)-1,10-phenanthroline complex **6** for amidation of iodobenzene with benzamide.[6c] The reaction works well in the presence of 8 mol % of catalyst, 2 equivalent K_3PO_4 in toluene at 110 °C (Scheme 8).



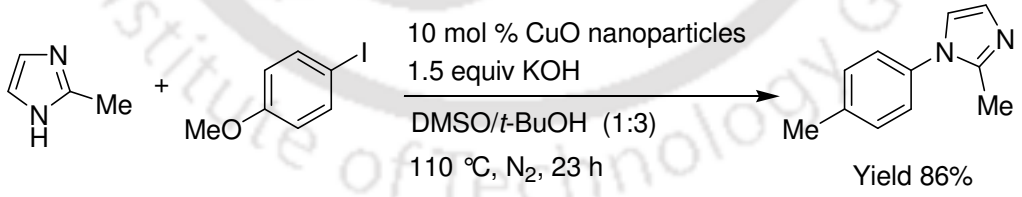
Scheme 8

Cu_2O with 4,7-dimethoxy-1,10–phenanthroline **9** has been employed by Buchwald and co-workers for arylation of imidazoles and benzimidazoles with aryl and heteroaryl iodides and bromides in combination in the presence of PEG and Cs_2CO_3 (Scheme 9).[6e]



Scheme 9

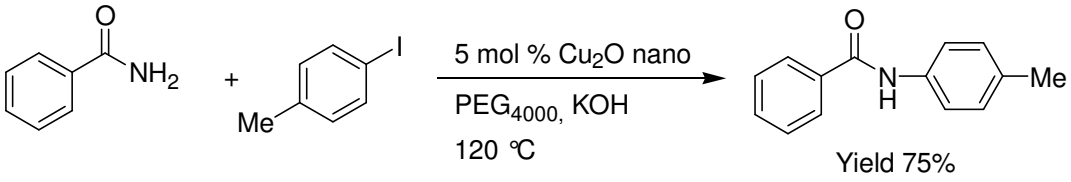
CuO-nanoparticles catalyzed *N*-arylations of amides and imdazoles with aryl iodides in presence of KOH at 110 °C have been discovered by our group.[5p-q] The procedure is simple, general, ligand-free and efficient to give the cross-coupled products in high yield (Scheme 10).



Scheme 10

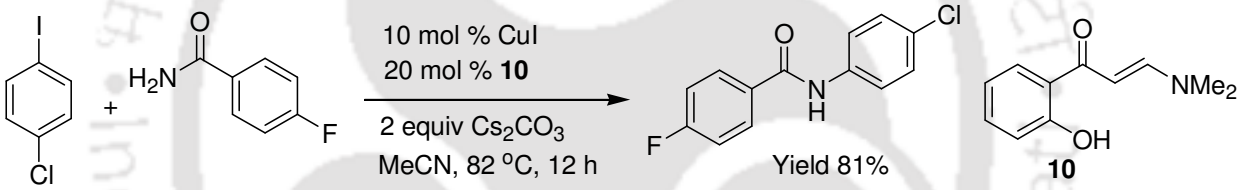
We have also developed a one pot procedure for the formation and catalysis of Cu_2O nanoparticles for the cross-coupling reactions of amides with aryl iodides in PEG_{4000} and KOH base in the absence of additional chelating ligand.[5r] The advantage of this method is

the catalyst could be recycled up 3rd cycle without significant loss of catalytic activity (Scheme 11).



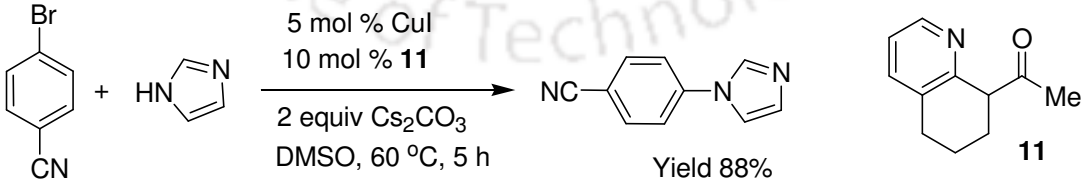
Scheme11

Sun and co-workers have used an enaminone **10** with CuI for *N*-arylation of amides and azoles in the presence of Cs_2CO_3 base in acetonitrile at 82 °C.[6q] In these conditions, a variety of azoles and amides undergo cross-coupling with aryl iodides and aryl bromides to provide the desired *N*-arylated products (Scheme 12).



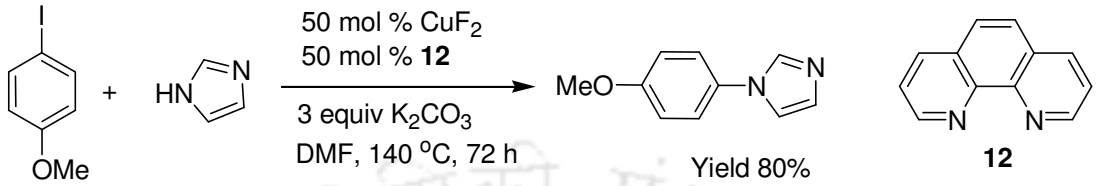
Scheme 12

Ding and co-workers have demonstrated an efficient copper(I) bromide and 1-(5,6,7,8-tetrahydroquinolin-8-yl)ethanone **11** system for the *N*-arylation of azoles with a variety of aromatic bromides and iodides (Scheme 13).[5s] The best result was obtained when the reaction was carried out with Cs_2CO_3 in DMSO at 60 °C under nitrogen atmosphere.



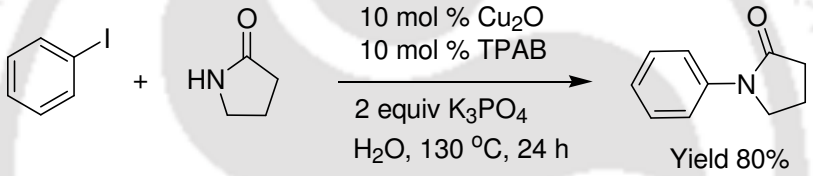
Scheme 13

Arylation of five-membered N-heterocycles was accomplished by Arsenyan and co-workers by using CuF_2 and 1,10-phenthroline **12** along with K_2CO_3 in DMF at 140 ˚C.[5t] The method is also used for the *N*-arylation azoles with iodothiophenes (Scheme 14).



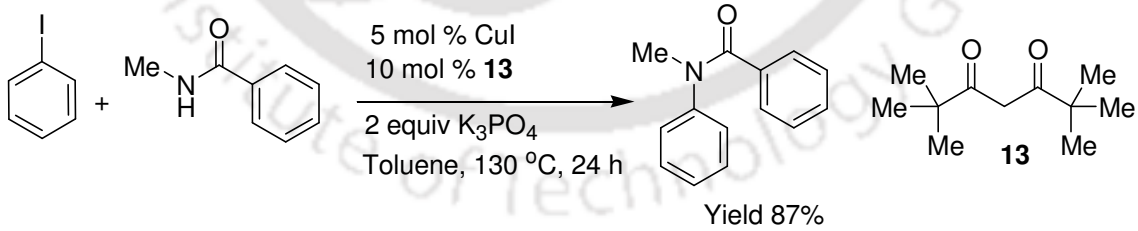
Scheme 14

N-Arylation of various amides with substituted aryl iodides by using a ligand free Cu_2O catalyst was described by Teo and co-workers.[6r] The reaction works in the presence of K_3PO_4 at 130 ˚C in water (Scheme 15).



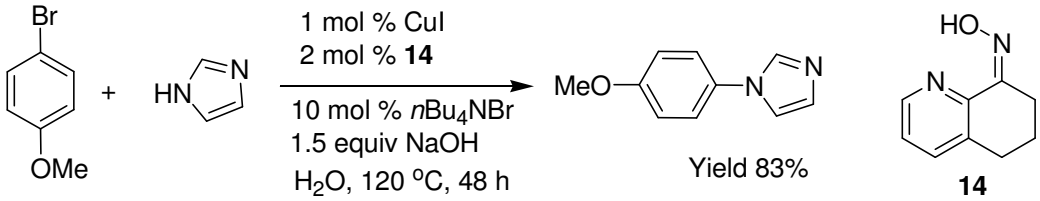
Scheme 15

N-Arylation of secondary acyclic amides has been accomplished by Marc Taillefer and co-workers using CuI and 1,3-diketone **13** along with K_3PO_4 in toluene at 130 ˚C.[6s] The N-arylated tertiary amides are obtained in good yield (Scheme 16).



Scheme 16

Wang and co-workers have developed a system for the arylation of imidazoles with CuI and 6,7-dihydroquinolin-8(5H)-one oxime **14** in water.[6t] A variety of aryl iodides, bromides, and electron-deficient chlorides undergo cross-coupling to provide N-arylated imidazoles and substituted imidazoles in good yields (Scheme 17).



Scheme 17

1.3 Present Study

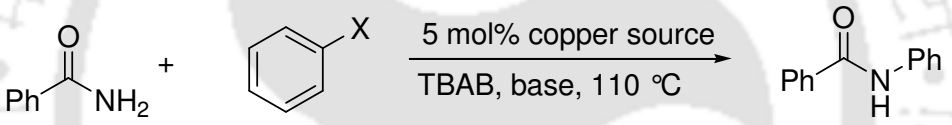
The use of molten salt for organic reactions has been active in recent years due to their excellent thermal stability and low vapor pressure.[7] In addition, the reactions in molten salts provide the advantages of high reactivity and simplified product isolation. More recently, tetrabutylammonium bromide (TBAB) has been found to be an effective reaction medium[8] as well as an additive[9] for the *C-C* and *C-S* cross-coupling reactions in the presence of transition metal salts. Since TBAB is cheap and readily available, we became further interested to investigate its application for organic synthesis. Herein, we report the *C-N* cross-coupling of amides and imidazoles with aryl halides using CuI in TBAB under air. The procedure is general, simple and efficient to avail the cross-coupled products under ligand-free conditions. Both the substrates having the electron withdrawing and -donating groups are compatible with this protocol to afford the *C-N* cross-coupled products in shorter time in high yields.

First, the reaction conditions were optimized studying the coupling of benzamide with aryl iodide as model substrate. The reaction occurred to afford the *C-N* cross-coupled *N*-phenylbenzamide in 75% yield when the substrates were stirred at 110 °C for 5 h using 5 mol % CuI and 2 equiv of KOH in TBAB under air (Table 1). Bases such as Cs_2CO_3 and K_2CO_3 were inferior to KOH providing the cross-coupled product in 18% and 12% yield, respectively. The reaction using CuI was more effective in comparison with other copper sources such as CuCl, CuBr, $CuCl_2{\cdot}2H_2O$, $CuSO_4{\cdot}5H_2O$, $Cu(OAc)_2{\cdot}H_2O$ and CuO nanoparticle. Of the aryl halides, aryl iodide exhibited greater reactivity. The reaction with less reactive aryl bromide required longer time to give the cross-coupled product in 50%

yield. In contrast, chlorobenzene showed no reaction. Similarly, the control experiment without either CuI or KOH exhibited no reaction.

Next, the scope of the procedure with respect to other substrates was studied (Table 2). Benzamide could be cross-coupled with aryl iodide having 2-OMe, 4-Br, 4-OMe, 4-Me and2,4-$(Me)_2$ substituents in 72-91% yield. Similarly, the reactions of benzamide having 3-Br, 3-NO_2, 4-OMe, 4-Me and 4-NO_2 substituents investigated with aryl iodide. As above, the reactions occurred efficiently to give the corresponding cross-coupled products in 58-79% yield. Aliphatic amides, acetamide, hexanamide and 2-oxazolidinone could be cross-coupled with aryl iodide in 75-87% yield. A similar result was obtained with (*E*)-cinnamamide and aryl iodide.

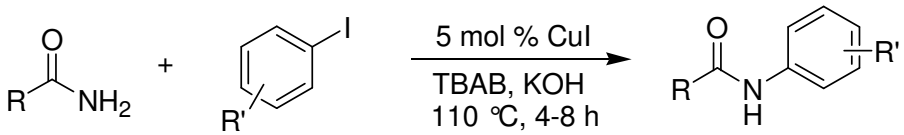
Table 1 Optimization of the reaction conditions[a,b]



Entry	Catalyst	X	Base	Time (h)	Yield (%)
1	CuI	I	KOH	5	75
2	CuI	I	Cs_2CO_3	7	18
3	CuI	I	K_2CO_3	9	12
4	CuI	Br	KOH	25	50
5	CuI	Cl	KOH	12	n.r[c]
6	CuCl	I	KOH	5	64
7	CuBr	I	KOH	5	59
8	$CuCl_2{\cdot}2H_2O$	I	KOH	6	57
9	$CuSO_4{\cdot}5H_2O$	I	KOH	6	61
10	$Cu(OAc)_2{\cdot}H_2O$	I	KOH	6	52
11	CuO nano	I	KOH	6	48

[a]Catalyst (5 mol %), benzamide (1.1 mmol), aryl halide (1 mmol) and base (2 mmol) were stirred at 110 °C in TBAB (2 mmol). [b]Isolated yield. [c]n.r. = no reaction.

Table 2 Reaction of amides with aryl iodides[a,b]



1a (5 h, 75%)

1b (8 h, 72%)

1c (5 h, 76%)

1d (6 h, 82%)

1e (5 h, 75%)

1f (6 h, 91%)

1g (6 h, 69%)

1h (7 h, 63%)

1i (5 h, 76%)

1j (4 h, 79%)

1k (6 h, 58%)

1l (4 h, 87%)

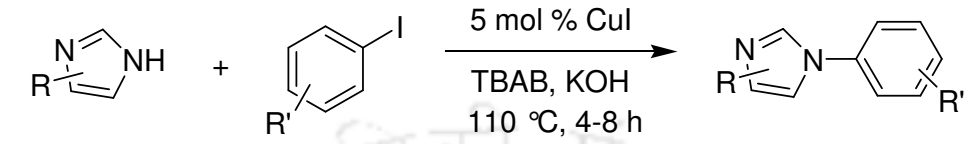
1m (4 h, 75%)

1n (5 h, 52%)

1o (4 h, 85%)

[a]CuI (5 mol %), amide (1.1 mmol), aryl iodide (1 mmol) and KOH (2 mmol) were stirred at 110 °C in TBAB (2 mmol). [b] Isolated yield.

Table 3 Reaction of imidazoles with aryl iodides[a,b]



2a (6 h, 85%)

2b (8 h, 55%)

2c (6 h, 93%)

2d (8 h, 70%)

2e (4 h, 95%)

2f (7 h, 65%)

2g (7 h, 78%)

2a (6 h, 72%)

[a]CuI (5 mol %), imidazole (1.1 mmol), aryl halide (1 mmol) and KOH (2 mmol) were stirred at 110 °C in TBAB (2 mmol). [b]Isolated yield.

These reaction conditions are also suitable for cross-coupling of imidazoles with aryl iodides. Imidazole could be cross-coupled with aryl iodide having 2-OMe, 4-OMe, 4-Me and 2,4-$(Me)_2$ substituents in 55-95% yield. Similarly, 2-methylimidazole and benzimidazole underwent reactions with aryl iodide in 78% and 72% yield respectively. The reactions required shorter time (4-8 h) and the cross-coupled products were obtained in high yield. Substituted aryl iodides as well as substituted amides and imidazoles were compatible with the procedure. These results clearly suggest that the reaction is general and can be used for the cross-coupling of amides and imidazoles with aryl iodides.

To study the reaction in more details we have isolated the catalyst after the completion of the reaction. The isolated catalyst was subjected to TEM and Powder XRD analyses (Figure 2). To our delight we have found the formation of CuO nanoparticles in the reaction medium. To explain the formation of CuO nanoparticles, we have proposed the following plausible pathway. The CuI can undergo reaction with KOH to provide Cu(OH) that could be transformed to CuO nanoparticles on air oxidation (Scheme 18).[10a-c] Here molten TBAB could play a dual role that it can act as a stabilizer of nanoparticles[10d] and ionic reaction medium.

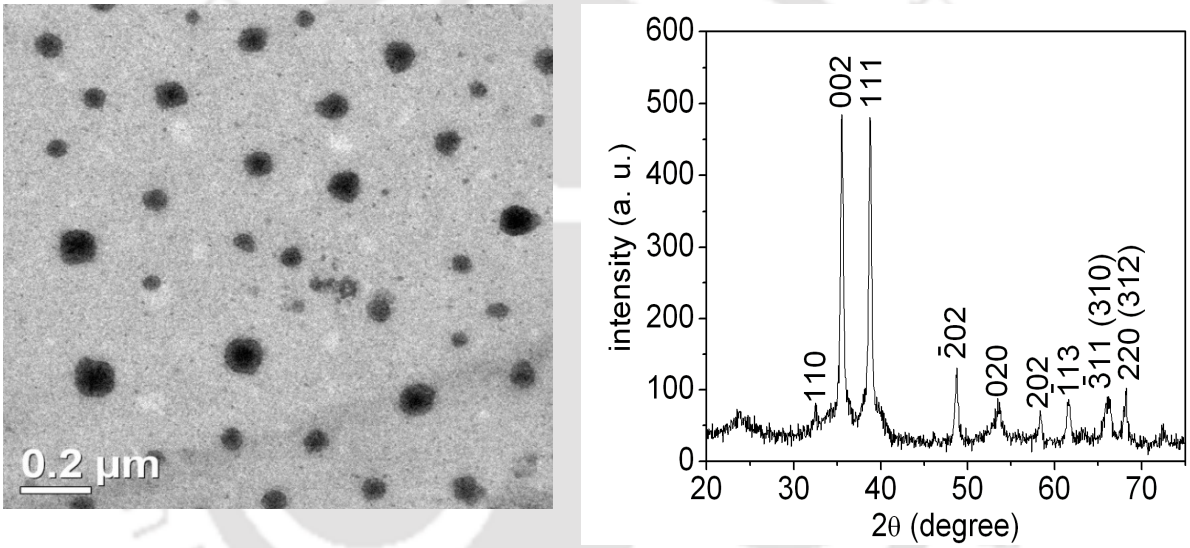
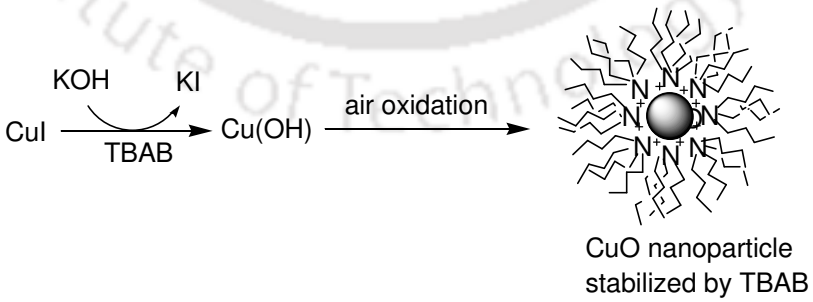


Figure 2 TEM image and Powder XRD of isolated CuO nanoparticles



Scheme 18

In summary, we have developed a simple and facile method for the *C-N* cross-coupling of amides and imidazoles with aryl iodides using CuI in TBAB under ligand-free conditions. The reactions are efficient affording the cross-coupled products in shorter time in high yields. Furthermore, we have also investigated that during the course of reaction in CuI converts to CuO nanoparticles.

Experimental Section

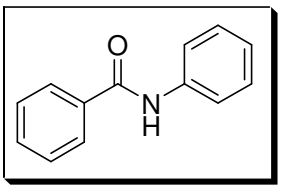
General Information

All chemicals were purchased from Aldrich and used without further purification. ^{1}H NMR (400 MHz) and ^{13}C NMR (100 MHz) spectra were recorded with a Varian 400 spectrometer. Infrared (IR) spectra were recorded on a Perkin Elmer FT-IR spectrophotometer. Melting points were determined with a Büchi B-545 apparatus and are uncorrected. Elemental analyses were recorded with Perkin Elmer CHNS analyzer.

General procedure for *C-N* cross-coupling reactions

An oven-dried round bottom flask was charged with the amide or imidazole (1.1 mmol), CuI (5 mol %), KOH (2.0 mmol), aryl halide (1.0 mmol) and TBAB (2.0 mmol) and the content was stirred at 110 ˚C for the appropriate time (Table 1-3). The reaction progress was monitored by TLC using ethyl acetate and hexane as eluent. The reaction mixture was then cooled to room temperature and diluted with EtOAc (10 mL). The resulting solution was washed with brine (2 mL) and water (2 x 2 mL). Drying (Na_2SO_4) and evaporation of the solvent gave a residue that was purified on silica gel column chromatography (230-400 mesh) using ethyl acetate and hexane as eluent to yield the *C-N* cross-coupled products.

Characterization Data of Products



***N*-Phenylbenzamide**[6b] (**1a**). Benzamide (133 mg, 1.1 mmol), CuI (9.5 mg, 5 mol %), KOH (112 mg, 2.0 mmol), iodobenzene (204 mg, 1.0 mmol) and TBAB (645 mg, 2.0 mmol) were subjected to the reaction conditions described in the general procedure to afford the title compound as white solid in 75 % (148 mg) yield.

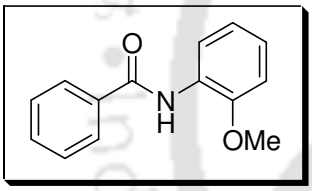
Mp: 162-163 °C (lit.[6b] 162-163 °C).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.86 (d, *J* = 7.2 Hz, 2H), 7.78 (br s, 1H), 7.63 (d, *J* = 8.0 Hz, 2H), 7.54 (d, *J* = 7.6 Hz, 1H), 7.47 (t, *J* = 8.0 Hz, 2H), 7.36 (t, *J* = 8.0 Hz, 2H), 7.14 (t, *J* = 7.2 Hz, 1H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 166.0, 138.1, 135.2, 132.0, 129.3, 128.9, 127.2, 124.8, 120.5.

FT-IR (KBr): 3310, 2995, 1659, 1604, 1533, 1420, 1315, 1233, 1185, 1090, 1023 cm^{-1}.

Anal. Calcd. for $C_{13}H_{11}NO$: C, 79.16; H, 5.62; N, 7.10. Found: C, 79.19; H, 5.63; N, 7.13.



***N*-(2-Methoxyphenyl)benzamide**[6j] (**1b**). Benzamide (133 mg, 1.1 mmol), CuI (9.5 mg, 5 mol %), KOH (112 mg, 2.0 mmol), 2-methoxyiodobenzene (234 mg, 1.0 mmol) and TBAB (645 mg, 2.0 mmol) were subjected to the reaction conditions described in the general procedure to afford the title compound as white solid in 72% (164 mg) yield.

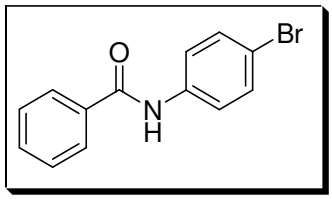
Mp: 58-59 °C (lit.[11a] 58-60 °C).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.54 (br s, 1H), 8.52-8.50 (dd, *J* = 1.6, 8 Hz, 1H), 7.89-7.86 (m, 2H), 7.55-7.45 (m, 3H), 7.09-7.05 (m, 1H), 7.02-6.98 (m, 1H) 6.90 (dd, *J* = 1.6, 8 Hz, 1H), 3.91 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 165.5, 148.4, 135.6, 131.9, 128.9, 128.0, 127.3, 124.1, 121.5, 120.1, 110.2, 56.0.

FT-IR (KBr): 3438, 2928, 1661, 1602, 1519, 1459, 1289, 1253, 1029 cm^{-1}.

Anal. Calcd. for $C_{14}H_{13}NO_2$: C, 73.99; H, 5.77; N, 6.16. Found: C, 74.04; H, 5.78; N, 6.19.



***N*-(4-Bromophenyl)benzamide**[12a] (**1c**). Benzamide (133 mg, 1.1 mmol), CuI (9.5 mg, 5 mol %), KOH (112 mg, 2.0 mmol), 4-bromoiodobenzene (283 mg, 1.0 mmol) and TBAB (645 mg, 2.0 mmol) were subjected to the reaction conditions described in the general procedure to afford the title compound as white solid in 76% (210 mg) yield.

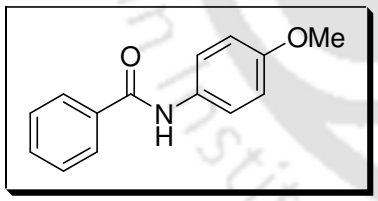
Mp: 202-203 °C (lit.[12a] 203-204 °C).

^{1}H NMR (400 MHz, $CDCl_3$:DMSO-d_6 (3:1)) δ 9.45 (br s, 1H), 7.65 (d, *J* = 8.4 Hz, 2H), 7.43 (d, *J* = 8.4 Hz, 2H), 7.24 (t, *J* = 8 Hz, 1H), 7.18 (d, *J* = 8 Hz, 2H), 7.16-7.12 (m, 2H).

^{13}C NMR (100 MHz, $CDCl_3$:DMSO-d_6 (3:1)): δ 166.1, 137.9, 134.8, 131.2, 131.1, 128.0, 127.4, 121.9, 115.9.

FT-IR (KBr): 3355, 3057, 2923, 2844, 1644, 1585, 1577, 1545, 1486, 1433, 1319, 1263, 1082, 1077, 1015 cm^{-1}.

Anal. Calcd. for $C_{13}H_{10}BrNO$: C, 56.55; H, 3.65; N, 5.07. Found: C, 56.59; H, 3.66; N, 5.12.



***N*-(4-Methoxyphenyl)benzamide**[11b] (**1d**). Benzamide (133 mg, 1.1 mmol), CuI (9.5 mg, 5 mol %), KOH (112 mg, 2.0 mmol), 4-methoxyiodobenzene (234 mg, 1.0 mmol) and TBAB (645 mg, 2.0 mmol) were subjected to the reaction conditions described in the general procedure to afford the title compound as white solid in 82% (186 mg) yield.

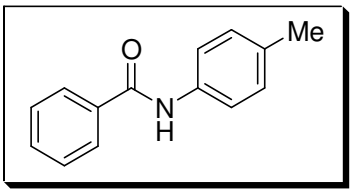
Mp: 157-158 °C (lit.[11c] 157-158 °C).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.85 (d, *J* = 8.0 Hz, 2H), 7.76 (s, 1H), 7.53-7.43 (m, 5H), 6.90 (d, *J* = 8.8 Hz, 2H), 3.79 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 165.9, 156.9, 135.2, 131.9, 131.3, 128.9, 127.2, 122.4, 114.5, 55.7.

FT-IR (KBr): 3330, 2963, 2926, 1646, 1514, 1469, 1413, 1261, 1095, 1026, 800 cm^{-1}.

Anal. Calcd. for $C_{14}H_{13}NO_2$: C, 73.99; H, 5.77; N, 6.16. Found: C, 74.05; H, 5.79; N, 6.15.



***N*-(4-Methylphenyl)benzamide**[11d] (**1e**). Benzamide (133 mg, 1.1 mmol), CuI (9.5 mg, 5 mol %), KOH (112 mg, 2.0 mmol), 4-methyliodobenzene (218 mg, 1.0 mmol) and TBAB (645 mg, 2.0 mmol) were subjected to the reaction conditions described in the general procedure to afford the title compound as white solid in 75% (158 mg) yield.

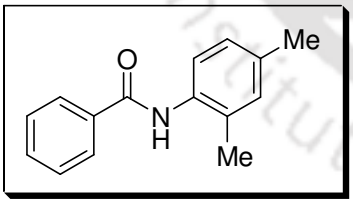
Mp: 158-159 °C (lit.[11c] 158-159 °C).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.84 (d, *J* = 8.4 Hz, 2H), 7.74 (br s, 1H), 7.54-7.44 (m, 5H), 7.16 (d, *J* = 8.4 Hz, 2H), 2.32 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 165.9, 135.6, 135.3, 134.4, 131.9, 129.8, 128.9, 127.2, 120.5, 21.1.

FT-IR (KBr): 3309, 2963, 2926, 2857, 1647, 1596, 1579, 1531, 1491, 1404, 1317, 1296, 1262, 1095, 1022 cm^{-1}.

Anal. Calcd. for $C_{14}H_{13}NO$: C, 79.59; H, 6.20; N, 6.63. Found: C, 79.64; H, 6.19; N, 6.67.



***N*-(2,4-Dimethylphenyl)benzamide** (**1f**). Benzamide (133 mg, 1.1 mmol), CuI (9.5 mg, 5 mol %), KOH (112 mg, 2.0 mmol), 2,4-dimethyliodobenzene (232 mg, 1.0 mmol) and TBAB (645 mg, 2.0 mmol) were subjected to the reaction conditions described in the general procedure to afford the title compound as white solid in 91% (205 mg) yield.

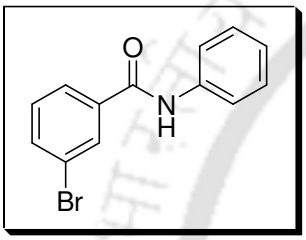
Mp: 193-194 °C (lit.[12b] 193-194 °C).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.86 (d, *J* = 7.2 Hz, 2H), 7.73 (d, *J* = 7.6 Hz, 1H), 7.58 (s, 1H), 7.55 (t, *J* = 7.6Hz, 1H), 7.47 (t, *J* = 7.8 Hz, 2H), 7.05 (d, *J* = 8.4 Hz, 2H), 2.30 (s, 3H), 2.27 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 165.9, 135.4, 135.2, 133.3, 131.9, 131.4, 129.9, 128.9, 127.6, 127.3, 123.8, 21.1, 17.9.

FT-IR (KBr): 3266, 2955, 2921, 2853, 1640, 1601, 1578, 1521, 1505, 1497, 1310, 1278, 1228, 1075, 1027 cm^{-1}.

Anal. Calcd. for $C_{15}H_{15}NO$: C, 79.97; H, 6.71; N, 6.22. Found: C, 79.99; H, 6.72; N, 6.26.



3-Bromo-*N*-phenylbenzamide[11e] (**1g**). 3-Bromobenzamide (220 mg, 1.1 mmol), CuI (9.5 mg, 5 mol %), KOH (112 mg, 2.0 mmol), iodobenzene (204 mg, 1.0 mmol) and TBAB (645 mg, 2.0 mmol) were subjected to the reaction conditions described in the general procedure to afford the title compound as white solid in 69% (191 mg) yield.

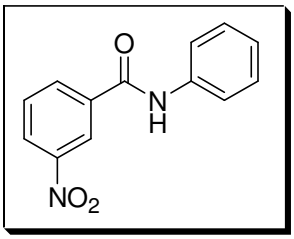
Mp: 142 ºC (lit.[11f] 142 °C).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.99 (s, 1H), 7.77 (d, *J* = 8.0 Hz, 2H), 7.67-7.60 (m, 3H), 7.38-7.33 (m, 3H), 7.16 (t, *J* = 7.6 Hz, 1H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 164.8, 137.7, 137.0, 134.9, 130.5, 130.4, 129.2, 125.9, 125.0, 122.9, 120.7.

FT-IR (KBr): 3341, 3054, 2927, 2846, 1654, 1599, 1567, 1533, 1492, 1440, 1320, 1257, 1094, 1073, 1023 cm^{-1}.

Anal. Calcd. for $C_{13}H_{10}BrNO$: C, 56.55; H, 3.65; N, 5.07. Found: C, 56.62; H, 3.63; N, 5.15.



3-Nitro-*N*-phenylbenzamide (**1h**). 3-Nitrobenzamide (183 mg, 1.1 mmol), CuI (9.5 mg, 5 mol %), KOH (112 mg, 2.0 mmol), iodobenzene (204 mg, 1.0 mmol) and TBAB (645 mg, 2.0 mmol) were subjected to the reaction conditions described in the general procedure to afford the title compound as light yellow solid in 63% (153 mg) yield.

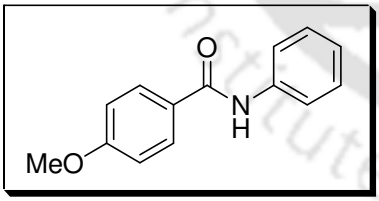
Mp: 153-154 ºC (lit.[12c] 154 °C).

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.68 (t, *J* = 2.0 Hz, 1H), 8.41-8.38 (m, 1H), 8.24 (d, *J* = 7.6 Hz, 1H), 7.96 (br s, 1H), 7.69 (t, *J* = 8.0 Hz, 1H), 7.63 (d, *J* = 8.0 Hz, 2H), 7.40-7.35 (m, 2H), 7.20-7.16 (m, 1H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 163.6, 148.4, 137.5, 136.8, 133.6, 130.3, 129.4, 126.6, 125.5, 122.1, 120.8.

FT-IR (KBr): 3318, 3084, 2963, 1657, 1619, 1600, 1529, 1444, 1351, 1325, 1262, 1095, 1026 cm^{-1}.

Anal. Calcd. for $C_{13}H_{10}N_2O_3$: C, 64.46; H, 4.16; N, 11.56. Found: C, 64.53; H, 4.18; N, 11.58.



4-Methoxy-*N*-phenylbenzamide[12d] (**1i**). 4-Methoxybenzamide (166 mg, 1.1 mmol), CuI (9.5 mg, 5 mol %), KOH (112 mg, 2.0 mmol), iodobenzene (204 mg, 1.0 mmol) and TBAB (645 mg, 2.0 mmol) were subjected to the reaction conditions described in the general procedure to afford the title compound as white solid in 79% (180 mg) yield.

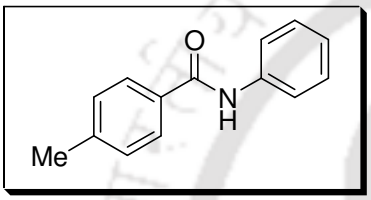
Mp: 171 ºC (lit.[12d] 170-171 °C).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.84-7.81 (m, 2H), 7.75 (br s, 1H), 7.61 (dd, *J* = 8.8 Hz, 0.8 Hz, 2H), 7.34 (dt, *J* = 2.0, 7.6 Hz, 2H), 7.12 (t, *J* = 7.6 Hz, 1H), 6.95 (dd, *J* = 2.4, 6.8 Hz, 2H), 3.85 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 165.7, 162.1, 138.7, 129.4, 128.7, 127.3, 123.9, 120.5, 113.5, 55.4.

FT-IR (KBr): 3338, 3081, 3052, 3020, 2959, 2934, 2839, 1655, 1597, 1579, 1528, 1507, 1463, 1437, 1325, 1312, 1250, 1181, 1106, 1027 cm^{-1}.

Anal. Calcd. for $C_{14}H_{13}NO_2$: C, 73.99; H, 5.77; N, 6.16. Found: C, 74.06; H, 5.75; N, 6.19.



4-Methyl-*N*-phenylbenzamide[12d] (**1j**). 4-Methylbenzamide (149 mg, 1.1 mmol), CuI (9.5 mg, 5 mol %), KOH (112 mg, 2.0 mmol), iodobenzene (204 mg, 1.0 mmol) and TBAB (645 mg, 2.0 mmol) were subjected to the reaction conditions described in the general procedure to afford the title compound as white solid in 76% (161 mg) yield.

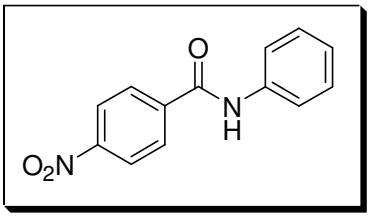
Mp: 149 ºC, (lit.[12d] 149-150 °C).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.75 (d, *J* = 8.4 Hz, 3H), 7.62 (d, *J* = 7.6 Hz, 2H), 7.35 (t, *J* = 8.4 Hz, 2H), 7.27 (d, *J* = 8.0 Hz, 2H), 7.12 (t, *J* = 7.6 Hz, 1H), 2.41 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 165.9, 142.6, 138.2, 132.3, 129.6, 129.3, 127.2, 124.6, 120.4, 21.7.

FT-IR (KBr): 3351, 3059, 2918, 2861, 1650, 1613, 1597, 1524, 1439, 1320, 1298, 1261 cm^{-1}.

Anal. Calcd. for $C_{14}H_{13}NO$: C, 79.59; H, 6.20; N, 6.63. Found: C, 79.66; H, 6.19; N, 6.69.



4-Nitro-*N*-phenylbenzamide[12d] (**1k**). 4-Nitrobenzamide (183 mg, 1.1 mmol), CuI (9.5 mg, 5 mol %), KOH (112 mg, 2.0 mmol), iodobenzene (204 mg, 1.0 mmol) and TBAB (645 mg, 2.0 mmol) were subjected to the reaction conditions described in the general procedure to afford the title compound as light yellow solid in 58% (140 mg) yield.

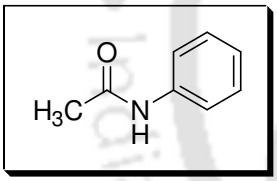
Mp: 215 ºC (lit.[12d] 217-218 °C).

^{1}H NMR (400 MHz, $CDCl_3$): δ 9.69 (br s, 1H), 8.18 (d, *J* = 7.2 Hz, 2H), 8.05 (d, *J* = 6.8 Hz, 2H), 7.63 (d, *J* = 8.0 Hz, 2H), 7.24 (t, *J* = 7.6 Hz, 2H), 7.03 (t, *J* = 7.2 Hz, 1H).

^{13}C NMR (100 MHz, $CDCl_3$:DMSO-d_6 (3:1)): δ 163.9, 149.1, 140.6, 138.1, 128.8, 128.5, 124.3, 123.1, 120.7.

FT-IR (KBr): 3322, 3075, 2924, 2853, 1652, 1597, 1533, 1519, 1494, 1441, 1348, 1325, 1263, 1107 cm^{-1}.

Anal. Calcd. for $C_{13}H_{10}N_2O_3$: C, 64.46; H, 4.16; N, 11.56. Found: C, 64.54; H, 4.14; N, 11.65.



***N*-Phenylacetamide**[12e] (**1l**). Acetamide (65 mg, 1.1 mmol), CuI (9.5 mg, 5 mol %), KOH (112 mg, 2.0 mmol), iodobenzene (204 mg, 1.0 mmol) and TBAB (645 mg, 2.0 mmol) were subjected to the reaction conditions described in the general procedure to afford the title compound as white solid in 87% (118 mg) yield.

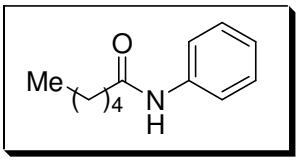
Mp: 161-163 °C (lit.[12e] 161-164 °C).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.85 (br s, 1H), 7.50 (d, *J* = 8 Hz, 2H), 7.30-7.25 (m, 2H), 7.08 (d, *J* = 7.6 Hz, 1H), 2.14 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 168.9, 138.2, 129.1, 124.5, 120.2, 24.7.

FT-IR (KBr): 3294, 3260, 3194, 3136, 3059, 3021, 2925, 2854, 2802, 1660, 1599, 1557, 1500, 1488, 1435, 1369, 1323, 1264, 1041, 1013 cm^{-1}.

Anal. Calcd. for C_8H_9NO: C, 71.09; H, 6.71; N, 10.36. Found: C, 71.13; H, 6.72; N, 10.42.



***N*-Phenylhexanamide**[12f] (**1m**). Hexanamide (127 mg, 1.1 mmol), CuI (9.5 mg, 5 mol %), KOH (112 mg, 2.0 mmol), iodobenzene (204 mg, 1.0 mmol) and TBAB (645 mg, 2.0 mmol) were subjected to the reaction conditions described in the general procedure to afford the title compound as white solid in 75% (143 mg) yield.

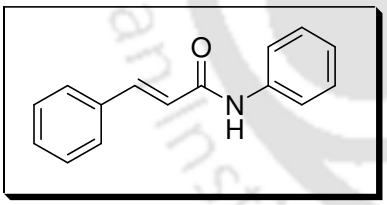
Mp: 93-94 °C (lit.[12g] 93-94 °C).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.48 (d, *J* = 7.6 Hz, 2H), 7.29 (t, *J* = 7.8 Hz, 2H), 7.14 (s, 1H), 7.07 (t, *J* = 8.0 Hz, 1H), 2.33 (t, *J* = 8.0 Hz, 2H), 1.73 (m, 2H), 1.34-1.33 (m, 4H), 0.90-0.87 (m, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 171.8, 138.2, 129.1, 124.4, 120.0, 38.0, 31.6, 25.5, 22.7, 14.1.

FT-IR (KBr): 3305, 3266, 3201, 3144, 3092, 2955, 2931, 2858, 1660, 1618, 1554, 1499, 1464, 1443, 1412, 1375, 1325, 1303, 1259, 1188 cm^{-1}.

Anal. Calcd. for $C_{12}H_{17}NO$: C, 75.35; H, 8.96; N, 7.32. Found: C, 75.39; H, 8.98; N, 7.30.



(*E*)-*N*-Phenylcinnamamide[11g] (**1n**). Cinnamamide (162 mg, 1.1 mmol), CuI (9.5 mg, 5 mol %), KOH (112 mg, 2.0 mmol), iodobenzene (204 mg, 1.0 mmol) and TBAB (645 mg, 2.0 mmol) were subjected to the reaction conditions described in the general procedure to afford the title compound as white solid in 52% (116 mg) yield.

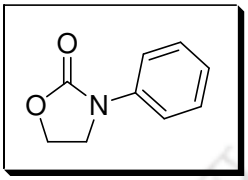
Mp: 151 ºC (lit.[11h] 151-153 °C).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.74 (d, *J* = 15.6 Hz, 1H), 7.61 (d, *J* = 7.2 Hz, 2H), 7.51 (dd, *J* = 3.2, 7.2 Hz, 2H), 7.46 (br s, 1H), 7.37-7.31 (m, 5H), 7.17 (t, *J* = 7.6 Hz, 1H), 6.55 (d, *J* = 15.2 Hz, 1H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 164.6, 142.5, 138.3, 134.8, 130.1, 129.2, 129.0, 128.1, 124.6, 121.2, 120.4.

FT-IR (KBr): 3436, 3271, 3129, 3035, 2961, 2925, 1661, 1625, 1595, 1546, 1494, 1443, 1350, 1294, 1251, 1189 cm^{-1}.

Anal. Calcd. for $C_{15}H_{13}NO$: C 80.69, H 5.87, N 6.27, found: C 80.75, H 5.90, N 6.32.



3-Phenyl-2-oxazolidinone[6b] (**1o**). 2-Oxazolidone (96 mg, 1.1 mmol), CuI (9.5 mg, 5 mol %), KOH (112 mg, 2.0 mmol), iodobenzene (204 mg, 1.0 mmol) and TBAB (645 mg, 2.0 mmol) were subjected to the reaction conditions described in the general procedure to afford the title compound as white solid in 85% (139 mg) yield.

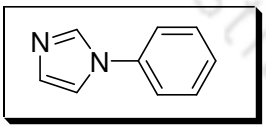
Mp: 120-121 °C (lit.[6b] 120 °C).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.51 (d, *J* = 7.6 Hz, 2H), 7.35 (t, *J* = 7.8 Hz, 2H), 7.13 (t, *J* = 7.2 Hz, 1H), 4.45 (t, *J* = 8.2 Hz, 2H), 4.03 (t, *J* = 8.0 Hz, 2H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 155.5, 138.4, 129.2, 124.2, 118.4, 61.5, 45.3.

FT-IR (KBr): 2923, 1736, 1610, 1520, 1500, 1404, 1316, 1262, 1122, 1089, 1020 cm^{-1}.

Anal. Calcd. for $C_9H_9NO_2$: C, 66.25; H, 5.56; N, 8.58. Found: C, 66.34; H, 5.59; N, 8.63.



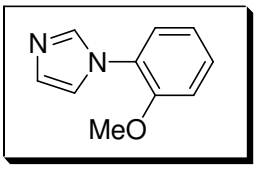
1-Phenyl-1*H*-imidazole[12e] (**2a**). Imidazole (75 mg, 1.1 mmol), CuI (9.5 mg, 5 mol %), KOH (112 mg, 2.0 mmol), iodobenzene (204 mg, 1.0 mmol) and TBAB (645 mg, 2.0 mmol) were subjected to the reaction conditions described in the general procedure to afford the title compound as yellow oil in 85% (123 mg) yield.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.83 (br s, 1H), 7.47-7.43 (m, 2H), 7.36-7.33 (m, 3H), 7.26 (br s, 1H), 7.18 (br s, 1H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 137.5, 135.8, 130.5, 130.1, 127.7, 121.7, 118.5.

FT-IR (KBr/neat): 3120, 3060, 1605, 1514, 1311, 1252, 1117, 1063, 968, 901, 811 cm^{-1}.

Anal. Calcd. for $C_9H_8N_2$: C, 74.98; H, 5.59; N, 19.43. Found: C, 74.99; H, 5.57; N, 19.44.



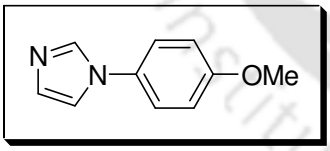
1-(2-Methoxyphenyl)-1*H*-imidazole[6i] (**2b**). Imidazole (75 mg, 1.1 mmol), CuI (9.5 mg, 5 mol %), KOH (112 mg, 2.0 mmol), 2-methoxyiodobenzene (234 mg, 1.0 mmol) and TBAB (645 mg, 2.0 mmol) were subjected to the reaction conditions described in the general procedure to afford the title compound as colorless oil in 55% (96 mg) yield.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.76 (s, 1H), 7.35-7.30 (m, 1H), 7.25-7.23 (m, 1H), 7.15 (d, *J* = 14.8 Hz, 2H), 7.03-6.98 (m, 2H), 3.81 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 152.8, 137.9, 129.2, 128.8, 126.6, 125.7, 121.2, 120.5, 112.5, 55.9.

FT-IR (KBr/neat): 3398, 2924, 2851, 1600, 1516, 1454, 1382, 1283, 1251, 1179, 1029 cm^{-1}.

Anal. Calcd. for $C_{10}H_{10}N_2O$: C, 68.95; H, 5.79; N, 16.08. Found: C, 68.99; H, 5.80; N, 16.13.



1-(4-Methoxyphenyl)-1*H*-imidazole[12e] (**2c**). Imidazole (75 mg, 1.1 mmol), CuI (9.5 mg, 5 mol %), KOH (112 mg, 2.0 mmol), 4-methoxyiodobenzene (234 mg, 1.0 mmol) and TBAB (645 mg, 2.0 mmol) were subjected to the reaction conditions described in the general procedure to afford the title compound as light yellow oil in 70% (122 mg) yield.

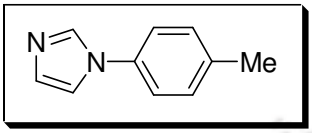
Mp: 62-63 °C (lit.[4k] 62-63 °C)

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.77 (br s, 1H) 7.28 (d, *J* = 8.8 Hz, 2H), 7.20 (br s, 2H), 6.96 (d, *J* = 9.2 Hz, 2H), 3.82 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 159.2, 136.0, 130.9, 130.1, 123.4, 119.0, 115.1, 55.8.

FT-IR (KBr/neat): 3325, 2924, 2846, 1599, 1519, 1462, 1382, 1300, 1251, 1182, 1059, 1028 cm^{-1}.

Anal. Calcd. for $C_{10}H_{10}N_2O$: C, 68.95; H, 5.79; N, 16.08. Found: C, 68.99; H, 5.81; N, 16.12.



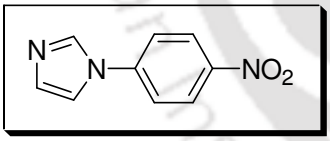
1-(4-Methylphenyl)-1*H*-imidazole[6i] (**2d**). Imidazole (75 mg, 1.1 mmol), CuI (9.5 mg, 5 mol %), KOH (112 mg, 2.0 mmol), 4-methyliodobenzene (218 mg, 1.0 mmol) and TBAB (645 mg, 2.0 mmol) were subjected to the reaction conditions described in the general procedure to afford the title compound as yellow oil in 93% (147 mg) yield.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.82 (s, 1H), 7.28-7.26 (m, 5H), 7.19 (s, 1H), 2.41 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): 137.7, 135.9, 135.3, 130.6, 130.4, 121.7, 118.6, 21.2.

FT-IR (KBr/neat): 3419, 2927, 2851, 1599, 1518, 1454, 1380, 1300, 1251, 1229, 1174, 1034 cm^{-1}.

Anal. Calcd. for $C_{10}H_{10}N_2$: C, 75.92; H, 6.37; N, 17.71. Found: C, 75.96; H, 6.35; N, 17.69.



1-(4-Nitrophenyl)-1*H*-imidazole[6i] (**2e**). Imidazole (75 mg, 1.1 mmol), CuI (9.5 mg, 5 mol %), KOH (112 mg, 2.0 mmol), 4-nitroiodobenzene (249 mg, 1.0 mmol) and TBAB (645 mg, 2.0 mmol) were subjected to the reaction conditions described in the general procedure to afford the title compound as yellow solid in 95% (180 mg) yield.

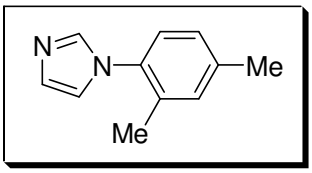
Mp: 203-205 °C (lit.[12h] 203-205 °C).

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.36 (d, J = 8.8 Hz, 2H), 7.96 (br s, 1H), 7.56 (d, J = 8.8 Hz, 2H), 7.36 (br s, 1H), 7.26 (br s, 1H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 146.4, 142.1, 135.6, 131.8, 125.9, 121.2, 117.8.

FT-IR (KBr): 3106, 2962, 2851, 1599, 1511, 1340, 1306, 1262, 1108, 1052 cm^{-1}.

Anal. Calcd. for $C_9H_7N_3O_2$: C, 57.14; H, 3.73; N, 22.21. Found: C, 57.18; H, 3.71; N, 22.25.



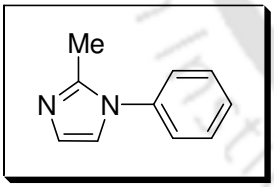
1-(2,4-Dimethylphenyl)-1*H*-imidazole (**2f**). Imidazole (75 mg, 1.1 mmol), CuI (9.5 mg, 5 mol %), KOH (112 mg, 2.0 mmol), 2,4-dimethyliodobenzene (232 mg, 1.0 mmol) and TBAB (645 mg, 2.0 mmol) were subjected to the reaction conditions described in the general procedure to afford the title compound as yellow oil in 65% (112 mg) yield.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.53 (s, 1H), 7.15 (s, 1H), 7.11 (s, 1H), 7.06 (s, 2H), 6.99 (s, 1H), 2.35 (s, 3H), 2.10 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 139.0, 137.8, 134.3, 133.8, 132.1, 129.4, 127.6, 126.6, 120.9, 21.2, 17.7.

FT-IR (KBr/neat): 3407, 2923, 2846, 1615, 1516, 1451, 1443, 1380, 1251, 1226, 1033 cm^{-1}.

Anal. Calcd. for $C_{11}H_{12}N_2$: C, 76.71; H, 7.02; N, 16.27. Found: C, 76.74; H, 7.01; N, 16.25.



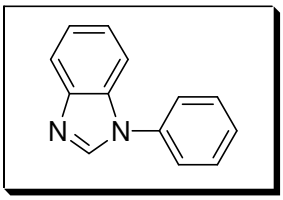
2-Methyl-1-phenyl-1*H*-imidazole[12i] (**2g**). 2-Methylimidazole (90 mg, 1.1 mmol), CuI (9.5 mg, 5 mol %), KOH (112 mg, 2.0 mmol), iodobenzene (204 mg, 1.0 mmol) and TBAB (645 mg, 2.0 mmol) were subjected to the reaction conditions described in the general procedure to afford the title compound as colorless oil in 78% (123 mg) yield.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.48-7.40 (m, 3H), 7.28-7.24 (m, 2H), 7.01 (d, J = 8.8 Hz, 2H), 2.34 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 144.9, 138.1, 129.7, 128.5, 127.6, 125.8, 120.9, 13.9.

FT-IR (KBr/neat): 3117, 3059, 1601, 1510, 1309, 1259, 1120, 1075, 989, 918, 801 cm^{-1}.

Anal. Calcd. for $C_{10}H_{10}N_2$: C, 75.92; H, 6.37; N, 17.71. Found: C, 75.98; H, 6.33; N, 17.69.



1-Phenyl-1*H*-benzimidazole[12e] (**2h**). Benzimidazole (130 mg, 1.1 mmol), CuI (9.5 mg, 5 mol %), KOH (112 mg, 2.0 mmol), iodobenzene (204 mg, 1.0 mmol) and TBAB (645 mg, 2.0 mmol) were subjected to the reaction conditions described in the general procedure to afford the title compound as yellow oil in 72% (140 mg) yield.

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.10 (s, 1H), 7.87-7.85 (m, 1H), 7.58-7.43 (m, 6H), 7.34-7.31 (m, 2H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 144.0, 142.4, 136.4, 133.8, 130.1, 128.1, 124.1, 123.1, 122.9, 120.6, 110.6.

FT-IR (KBr/neat): 3406, 3065, 2927, 2846, 1599, 1503, 1454, 1382, 1319, 1286, 1248, 1231, 1201, 1028 cm^{-1}.

Anal. Calcd.for $C_{13}H_{10}N_2$: C, 80.39; H, 5.19; N, 14.42. Found: C, 80.44; H, 5.16; N, 14.40.

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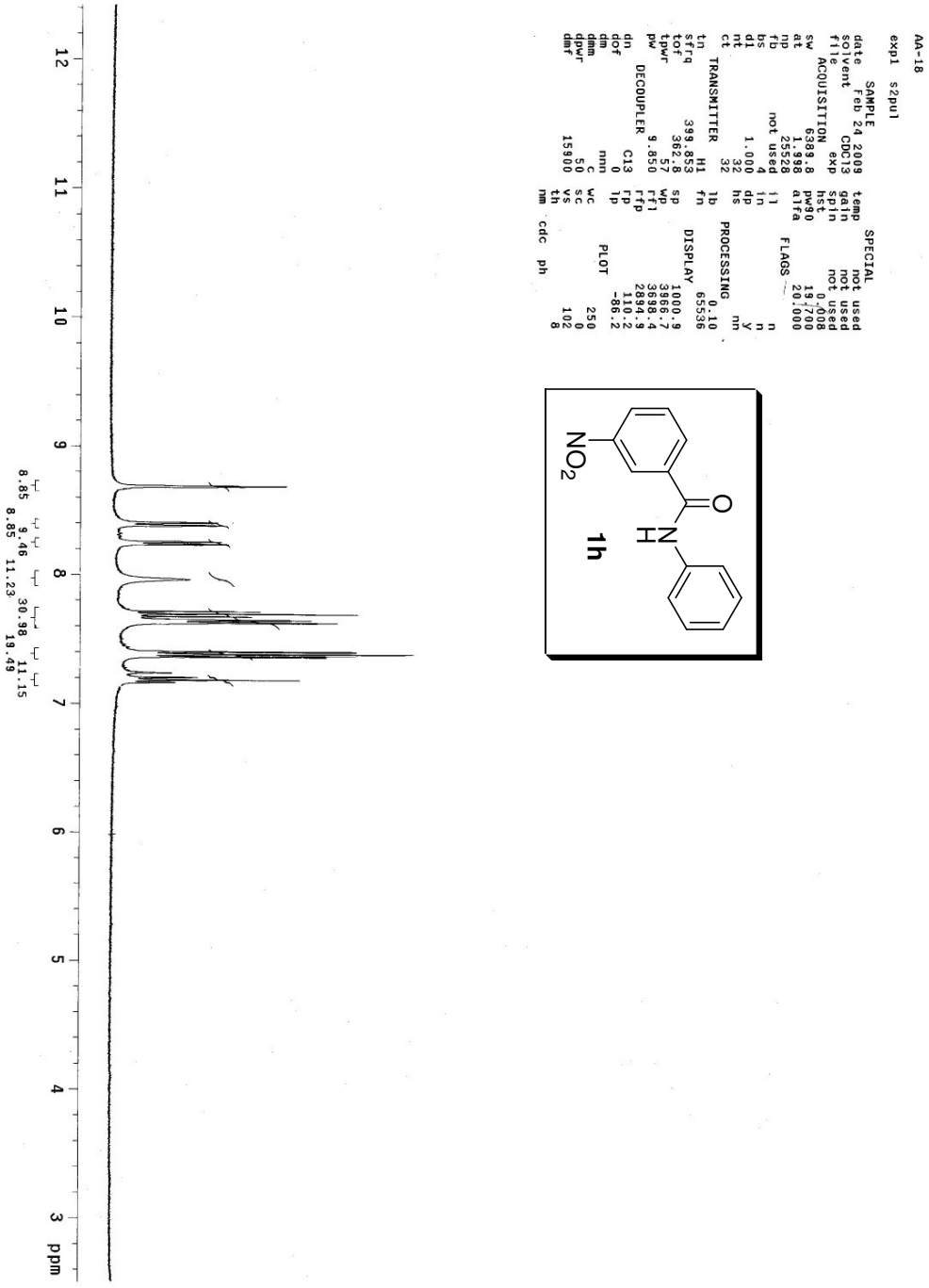
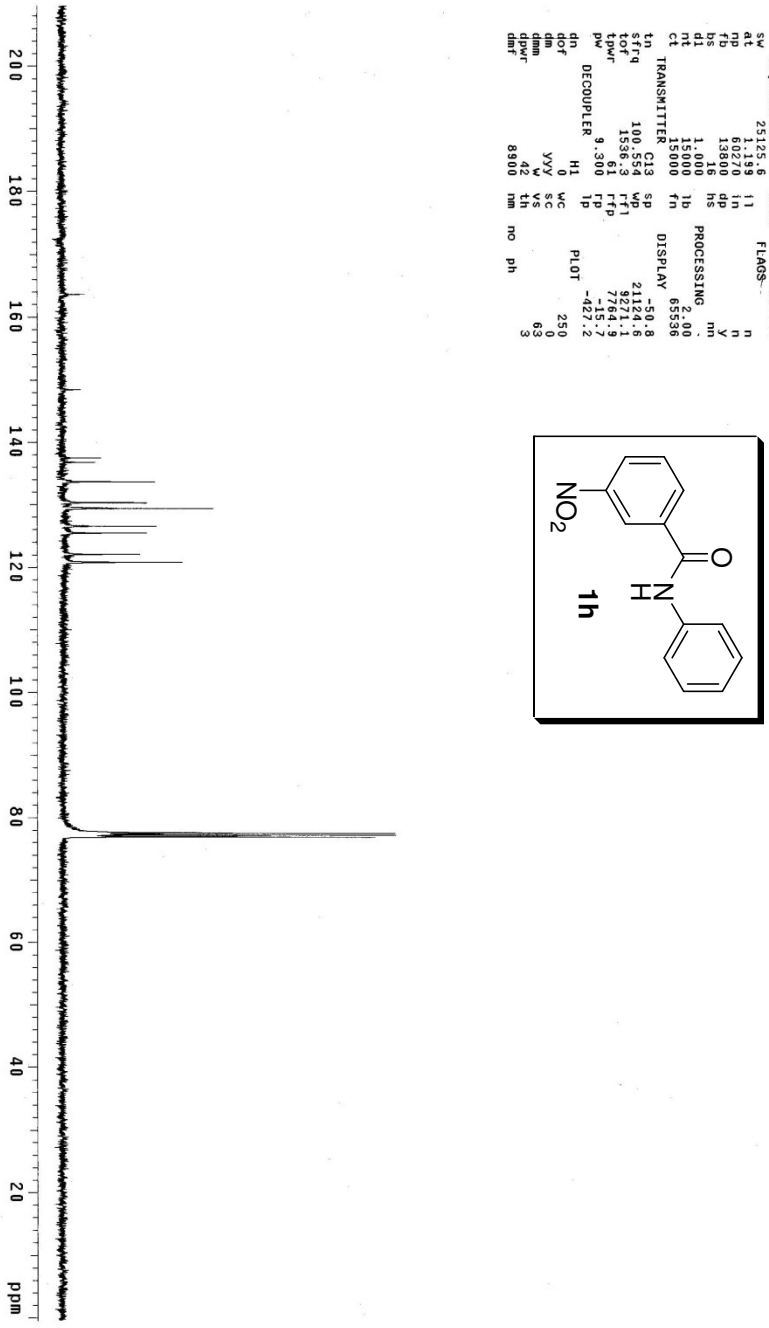
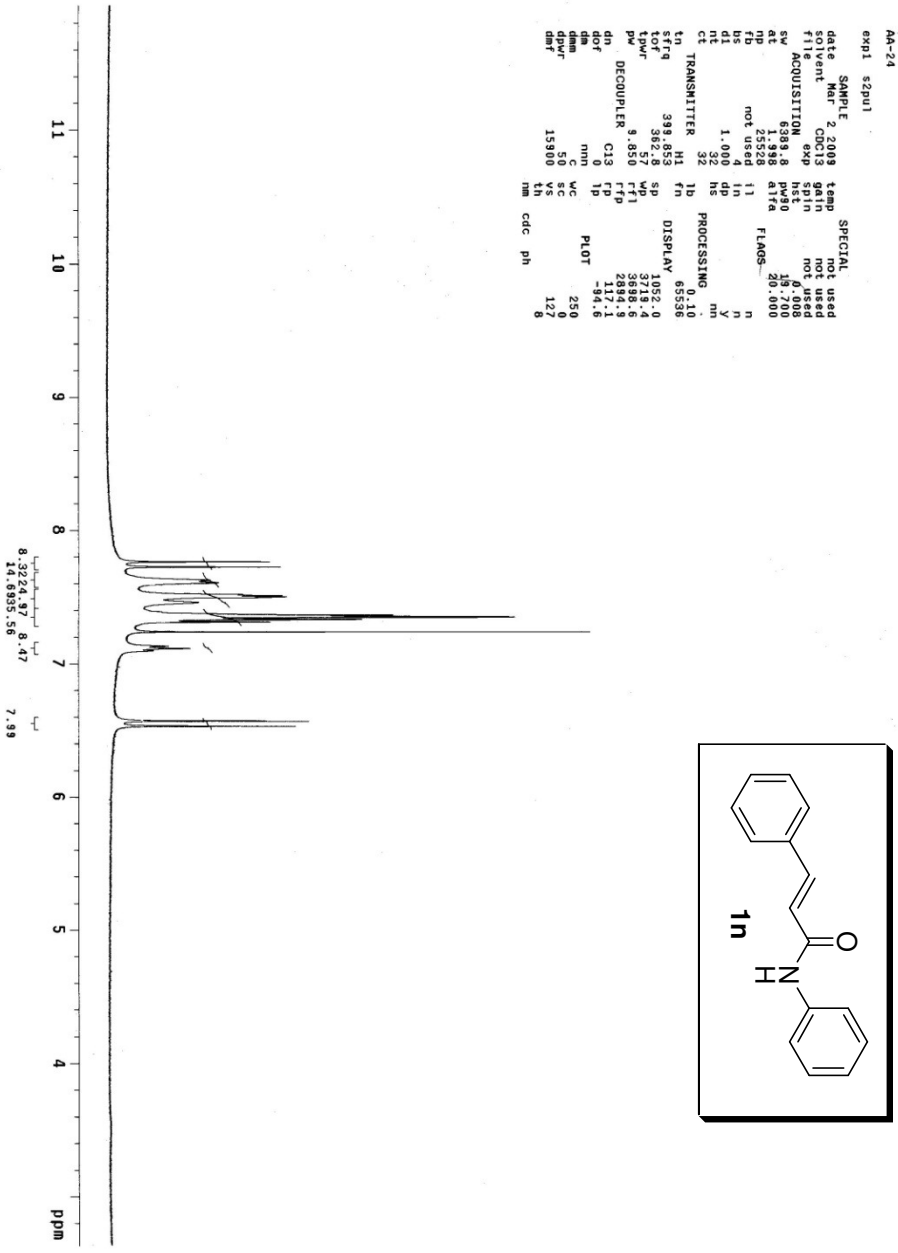
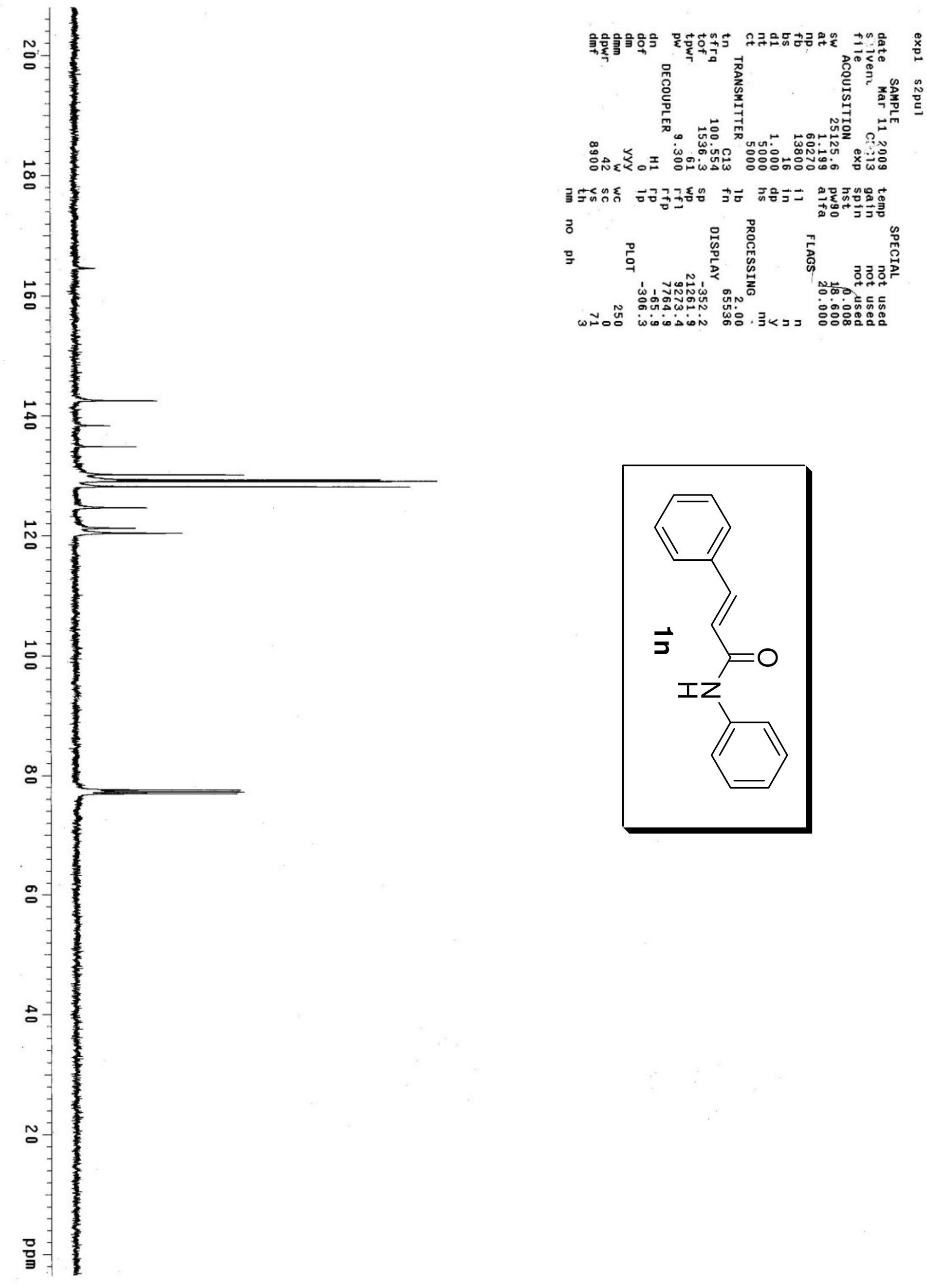








Chapter II

Domino CuI-Catalyzed Synthesis of 2-Arylbenzoxazoles

Benzoxazole moieties are an important class of heterocycles present in various natural products and biologically active compounds (Figure 1).[1] Recent research reveals the biological activity of benzoxazoles derivatives, for example 5-HT3 receptor agonist,[2a] HIV reverse transcriptase inhibitor L-697,661,[2b] selective peroxisome proliferator-activated receptor γ antagonist JTP-426467,[2c] anticancer agent NSC-693638,[2d] orexin-1 receptor antagonist SB-334867,[2e] estrogen receptor-β agonist ERB-041,[2f] and Rho kinase inhibitors.[2g] Benzoxazoles derivatives are well known for their antimicrobial,[3a] antiviral[3b] and anti-inflamatory[3c] activities and are used to treat immune diseases,[3d] cerebral ischaemia[3e] and duchenne muscular dystrophy[3f] and also used as herbicides, such as fenoxaprop and as fluorescent whitening agent dyes, such as bisbenzoxazolyl ethylenes and arenes.[3g] Therefore, development of new strategically important methods for the synthesis of benzoxazole derivatives is in high priority to synthetic organic chemists.

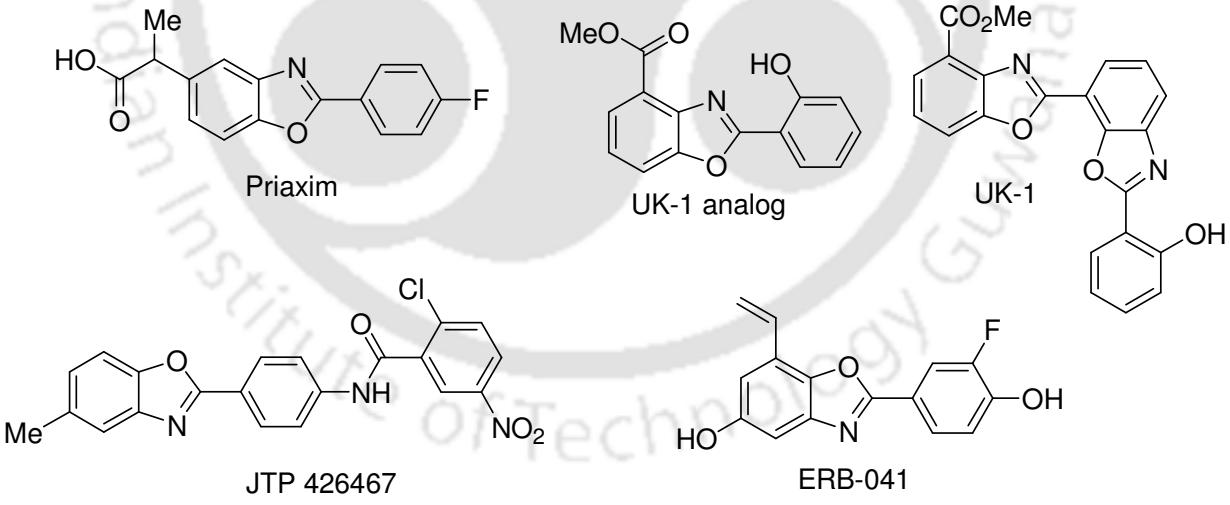


Figure 1 Examples of some biologically active compounds and natural products

The classical method for the benzoxazoles synthesis involves the condensation of *o*-aminophenols either with carboxylic acid under strong acidic conditions (Figure 2, path a)[4] or with aldehydes followed by oxidation with stoichiometric amount of the oxidizing

reagents[5a-h] or involves oxidation with molecular oxygen in the presence of some catalysts[5i-l] (Figure 2, path b). These protocols suffer from non availability of suitable substituted *o*-aminophenols and some with harsh reaction conditions such as requirement of strong acid or stoichiometric oxidizing agents.

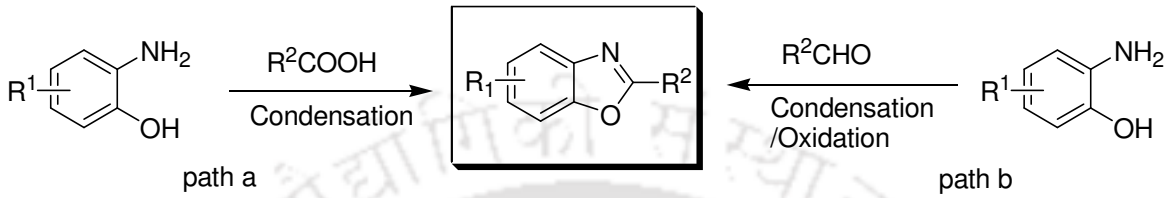
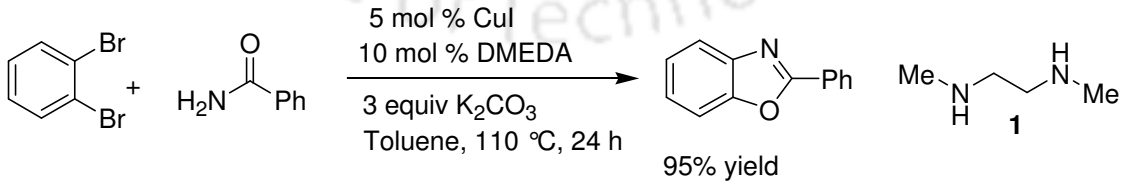


Figure 2 Classical methods for the synthesis of benzoxazole derivatives

To overcome these drawbacks, much attention has been recently focused for the development of new methods for the synthesis of benzoxazoles under relatively milder conditions. In this purpose the milder and efficient carbon-heteroatom cross-coupling methods have been used for the synthesis and functionalization of benzoxazoles for the past few years.

2.1 Copper catalysts

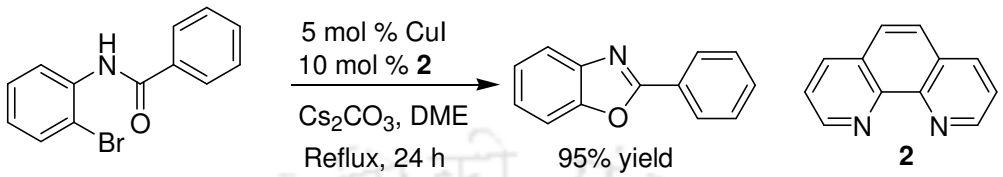
Copper catalyzed carbon heteroatom cross-coupling protocols have been used for the synthesis and functionalization of benzoxazoles derivatives. Altenhoff and Glorius reported the synthesis of benzoxazoles by using domino inter- and intramolecular *C–N* and *C–O* cross-coupling reactions of *o*-dihalobenzene with primary amides (Scheme 1).[6a] The reaction undergoes well in the presence of CuI and *N,N′*-dimethylethylenediamine (DMEDA) **1** in toluene at 110 ˚C to provide the desired benzoxazoles in good yields.



Scheme 1

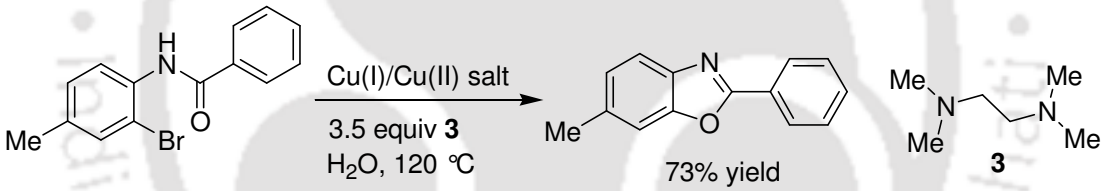
Batey and co-workers have used copper catalyzed intramolecular *C-O* bond formation strategy for the synthesis of benzoxazoles from *o*-halobenzanilides in the presence of CuI

and 1,10-phenanthroline **2** and Cs_2CO_3 in DME under reflux condition (Scheme 2).[6b-c] Under these conditions a variety of *o*-halobenzanilides undergo cyclization to give the target benzoxazoles in good yields.



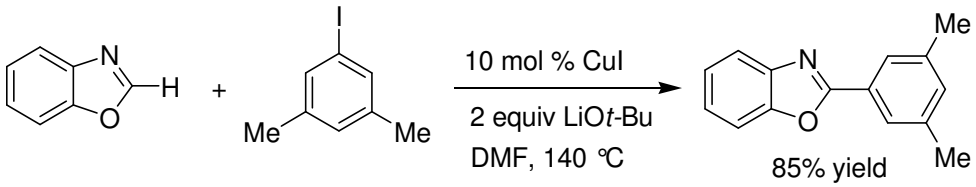
Scheme 2

Dominguez and co-workers have demonstrated the synthesis of benzoxazoles by using copper catalyzed *C-O* bond formation protocol. The reaction involves the use of Cu(I) or Cu(II) catalyst along with tetramethylethylenediamine (TMEDA) **3** in the presence of base in water at 120 ˚C (Scheme 3).[6d] *o*-Bromo- and *o*-chlorobenzanilides give better results compared to *o*-iodobenzanilides.



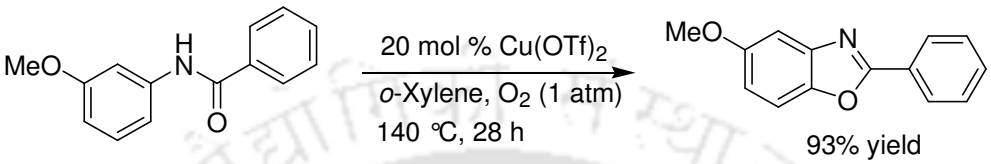
Scheme 3

A direct *C-H* functionalization and *C-C* bond formation protocol has been used for 2-arylation of benzoxazoles with aryl iodides (Scheme 4).[6e] This method involves the use of CuI as catalyst and lithium *tert*-butoxide as a base in DMF at 140 ˚C. The electron-rich five-membered heterocycles and electron-poor pyridine oxides can also be arylated by using the reaction conditions.



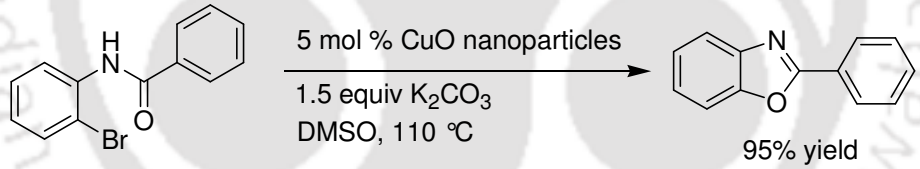
Scheme 4

Ueda and Nagasawa have discovered the synthesis of 2-arylbenzoxazoles from benzanilides via intramolecular regioselective *C-H* functionalization/*C-O* bond formation protocol in the presence of $Cu(OTf)_2$ as a catalyst in *o*-xylene at 140 ˚C under oxygen atmosphere (Scheme 5).[6f-g]



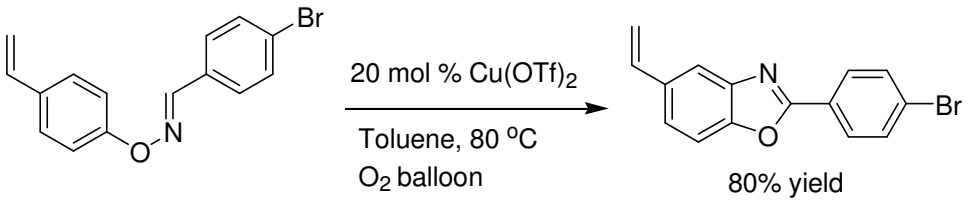
Scheme 5

We have developed a recyclable CuO nanoparticles catalyzed *C-O* cross-coupling protocol for synthesis of 2-aryl and 2-alkylbenzoxazoles from *o*-halobenzanilides under ligand free conditions (Scheme 6).[6h] The reactions are simple, general and efficient and the catalyst can be recovered and recycled up to 5th cycle without significant loss of catalytic activity and selectivity. We have successfully applied this reaction for gram scale synthesis of benzoxazoles.[6i]



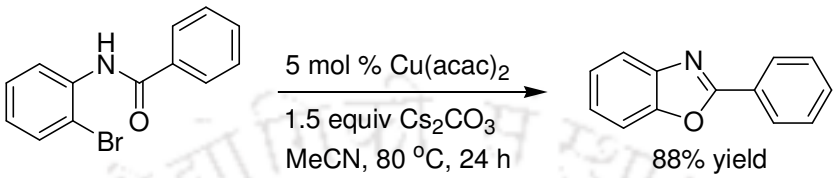
Scheme 6

Recently, we have discovered a cascade *C-H* functionalization and *C-N/C-O* bonds formation methods for the synthesis of 2-arylbenzoxazoles from bisaryloxime ethers in presence of $Cu(OTf)_2$ in toluene at 80 ˚C (Scheme 7).[6j-k] A variety of bisaryloxime ethers undergo the reaction to provide the desired benzoxazoles in good yields.



Scheme 7

Bhanage and co-workers have reported $Cu(acac)_2$-catalyzed cyclization of *N*-(2-bromophenyl)benzamide in the presence of Cs_2CO_3 in acetonitrile at 80 ˚C in 88% yield (Scheme 8).[61] The corresponding *o*-iodo and *o*-chloro substrates give 92% and 33% yield, respectively.



Scheme 8

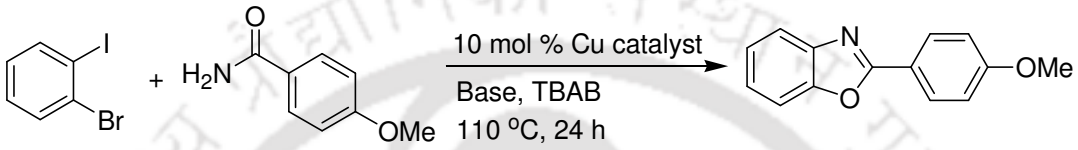
2.2 Present study

After being successful in CuI-catalyzed *N*-arylation of amides and imidazoles with aryl iodides in tetrabutylammonium bromide (TBAB) and our previous interest in synthesis of benzoxazoles, we were further interested to investigate the synthesis of benzoxazoles from 2-bromoiodobenzenes and primary amides. The reaction conditions were optimized by using 4-methoxybenzamide and 2-bromoiodobenzene as standard substrates (Table 1). When 2- bromoiodobenzene was treated with 4-methoxybenzamide in the presence of 10 mol % CuI and 2.5 equivalents of KOH in TBAB at 110 ˚C, with our excitement, the reaction provided the corresponding 2-(4-methoxyphenyl)benzoxazole in 65% yield. Increase or decrease in the amount of KOH or decrease in reaction temperature (100 ˚C), resulted in decrease in the amount of product formed. Similarly use of Cs_2CO_3 as a base or a 1:1 mixture of Cs_2CO_3 and KOH as a base, in both the cases the amount of product formation was decreased (17-22%). When the reaction was carried out by using CuO nanoparticles and commercially available Cu_2O as catalysts in TBAB, it provided only 25-27% of the desired product.

With the optimized reaction conditions in hand, next the scope of the procedure was explored with a variety of substituted benzamides and 2-bromoiodobenzenes (Table 2). For example, 2-bromoiodobenzene was successfully cross-coupled with benzamides having substituents such as 2-Me, 3-Cl, 3-Me, 4-Br, 4-Cl and 4-Me to give the benzoxazoles **2a-h** in 55-75% yields. Similarly, 2-bromoiodobenzene having substituents

such as 4-^{i}Pr, 4-OMe and 4-Me underwent reactions with benzamide to provide the benzoxazoles **2i-k** in 43-68% yield. Furthermore, the substituted 2-bromoiodobenzenes were successfully cross-coupled with substituted benzamides. For example, 2-bromo-4-isopropyliodobenzene was cross-coupled with benzamides having 4-Br, 4-OMe and 4-Me

Table 1 Optimization of Reaction Conditions[a,b]

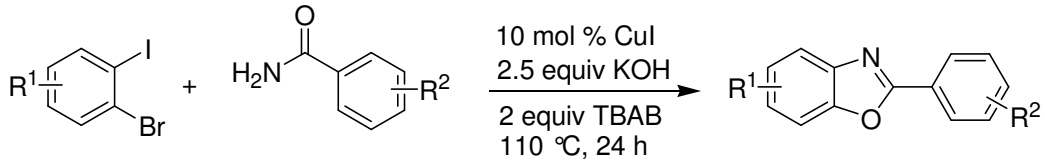


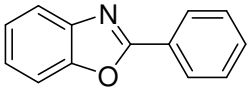
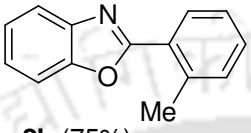
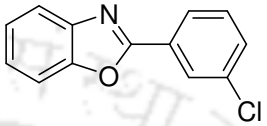
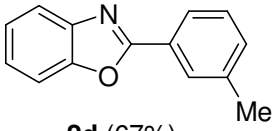
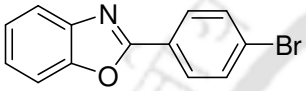
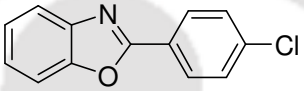
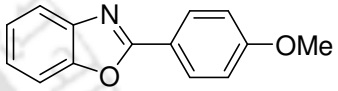
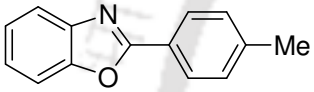
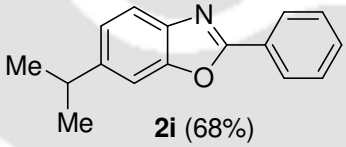
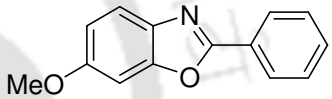
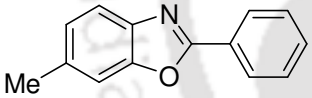
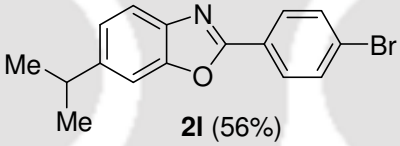
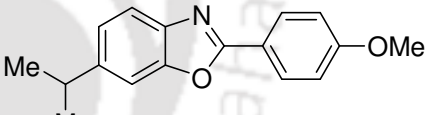
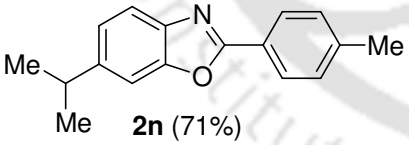
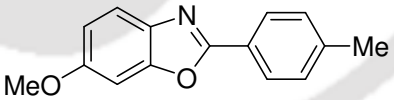
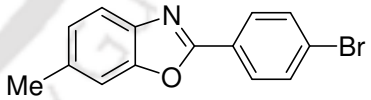
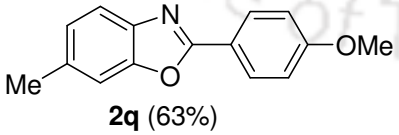
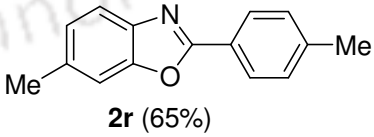
Entry	Catalyst	Base (equiv)	Yield (%)
1	CuI	KOH (2)	41
2	Cu_2O	KOH (2)	27
3	CuO (nano)	KOH (2)	25
4	CuI	KOH (2.5)	65
5	CuI	Cs_2CO_3 (2.5)	17
6	CuI	KOH (1.5):Cs_2CO_3 (1.5)	22
7	CuI	KOH (3)	61
8	CuI	KOH (2.5)	45[c]
9	CuI	KOH (2.5)	29[d]
10	-	KOH (2.5)	n.d.

[a]4-Methoxy benzamide (1.0 mmol), 2-bromoiodobenzene (1.0 mmol) catalyst (10 mol %) in appropriate medium was stirred for 24 h at 110 °C under nitrogen atmosphere. [b]Isolated yield. [c]Reaction was carried out at 100°C. [d]Reaction was carried out under air. n.d. = not detected.

substituents in 56-71% yields. Likewise, 2-bromo-4-methoxyiodobenzene and 2-bromo-4-methyliodobenzene reacted with benzamides having substituents such as 4-Br, 4-OMe and 4-Me to provide the benzoxazoles **2o-r** in 49-65% yields. The reaction of 2-bromoiodobenzene with aliphatic amide such as propanamide failed to give the corresponding benzoxazole under similar reaction conditions.

Table 2 Reaction of 2-iodobenzenes with amides[a,b]

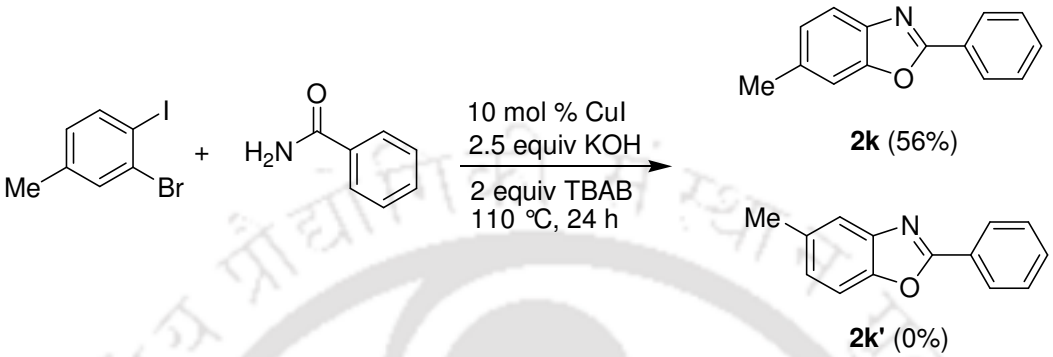


 **2a** (61%)	 **2b** (75%)	 **2c** (57%)	 **2d** (67%)
 **2e** (55%)	 **2f** (53%)	 **2g** (65%)	
 **2h** (60%)	 **2i** (68%)	 **2j** (43%)	
 **2k** (56%)	 **2l** (56%)	 **2m** (62%)	
 **2n** (71%)	 **2o** (49%)	 **2p** (50%)	
 **2q** (63%)	 **2r** (65%)		

[a]Benzamides (1.0 mmol), 2-bromoiodobenzenes (1.0 mmol), CuI (10 mol %) KOH (2.5 mmol) and TBAB (2.0 mmol) were stirred for 24 h at 110 ˚C. [b]Isolated yield.

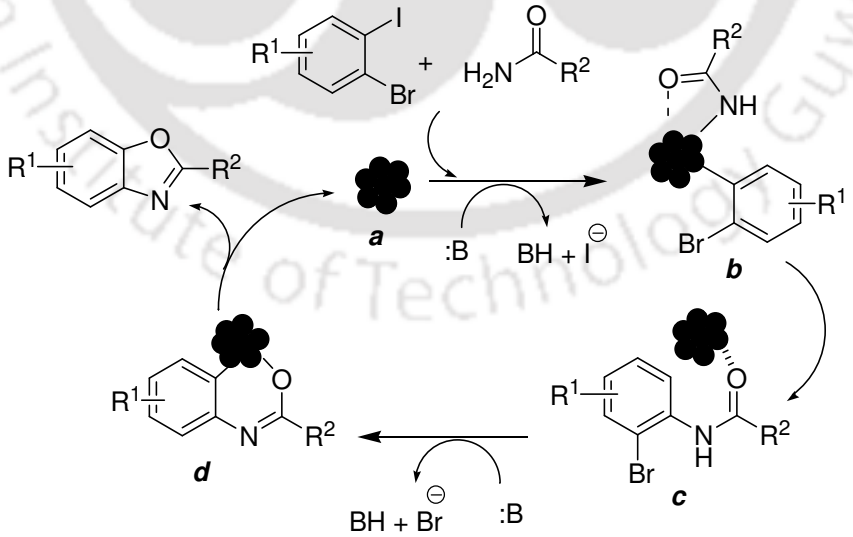
The advantage of this method is it gives only one regioisomer specifically eliminating the other possible regioisomer. For example, when 2-bromo-4-methyliodobenzene and

benzamide were subjected to the reaction conditions, 6-methyl-2-phenylbenzoxazole **2k** was obtained as a sole product and the formation of the other regioisomer, 5-methyl-2-phenylbenzoxazole **2ḱ**, was not observed (Scheme 9).



Scheme 9

In this reaction conditions, the CuI in situ converts to CuO nanoparticles which can catalyze the reaction. The CuO nanoparticles ***a*** in presence of base may undergo reaction with the substrate on their surface to generate intermediate ***b*** and the positive charge developed could be shared among the CuO nanoparticles present on the surface of the cluster (Scheme 10). The intermediate ***b*** can transform to intermediate ***c*** via C-N bond formation. The intermediate ***c*** similarly in the presence of base can transform to intermediate ***d*** which can regenerate the catalyst after reductive elimination of the product.



Scheme 10

In summary, we have developed a domino *C-N/C-O* bonds formation protocol for the synthesis of substituted 2-arylbenzoxazoles from 2-bromoiodobenzenes and substituted aromatic primary amides. The reaction is simple, general and free from addition of organic solvents. Further, the reactions are regiospecific providing one regioisomer exclusively.

Experimental Section

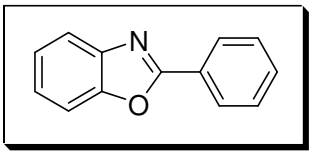
General Information

All the chemicals were purchased from Aldrich and used without further purification. The column chromatography was performed with Rankem silica gel (60-120 mesh). NMR spectra (400 MHz for ^{1}H and 100 MHz for ^{13}C) were recorded using DRX-400 Varian spectrometer using $CDCl_3$ and DMSO-d_6 as solvent and Me_4Si as internal standard. Chemical shifts (δ) are reported in ppm and spin-spin coupling constants (J) are given in Hz. Melting points were determined using Buchi B-540 melting point apparatus and are uncorrected. FT-IR spectra were recorded using Perkin Elmer IR spectroscopy. Elemental analyses were recorded using Perkin Elmer CHNS analyzer.

General Procedure for Synthesis of 2-arylbenzoxazoles

An oven-dried 10 mL round bottom flask was charged with the amides (1.0 mmol), 2-bromoiodobenzenes (1.0 mmol), CuI (10 mol %), KOH (2.5 mmol) and TBAB (2.0 mmol). The reaction mixture was placed in a preheated oil bath at 110 ˚C and stirred under nitrogen atmosphere for 24 h. The progress of the reaction was monitored by TLC. After completion, the reaction mixture was cooled to room temperature and then diluted with ethyl acetate (10 mL). The resulting solution was washed with water (2 x 10 mL). Drying (Na_2SO_4) and evaporation of the solvent gave a residue that was purified by silica gel column chromatography using (1-10%) ethyl acetate in hexane as eluent.

Characterization Data of Products



2-Phenylbenzoxazole[6b] **(2a)**: Benzamide (121 mg, 1.0 mmol), 2-bromoiodobenzene (283 mg, 1.0 mmol), CuI (19 mg, 10 mol %), KOH (140 mg, 2.5 mmol) and TBAB (645 mg, 2.0 mmol) were subjected to the reaction conditions described in the general procedure to afford the title compound as white solid in 61% (119 mg) yield.

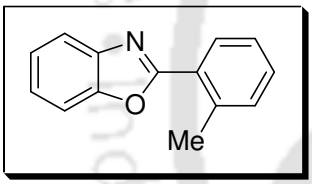
Mp: 101-102 ˚C (lit.[6b] 101-102 ˚C)

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.26-8.23 (m, 2H), 7.78-7.75 (m, 1H), 7.58-7.5.55 (m, 1H), 7.53-7.50 (m, 3H), 7.36-7.32 (m, 2H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 162.9, 150.7, 142.1, 131.4, 128.8, 127.6, 127.1, 125.1, 124.5, 120.0, 110.6.

FT-IR (KBr): 3060, 2961, 1616, 1552, 1472, 1447, 1344, 1241, 1196, 1052, 1022, 942 cm^{-1}.

Anal. Calcd. for $C_{13}H_9NO$: C, 79.98; H, 4.65; N, 7.17. Found: C, 80.05; H, 4.68; N, 7.12.



2-(2-Methylphenyl)benzoxazole[6g] **(2b)**: 2-Methylbenzamide (135 mg, 1.0 mmol), 2-bromoiodobenzene (283 mg, 1.0 mmol), CuI (19 mg, 10 mol %), KOH (140 mg, 2.5 mmol) and TBAB (645 mg, 2.0 mmol) were subjected to the reaction conditions described in the general procedure to afford the title compound as light yellow solid in 75% (157 mg) yield.

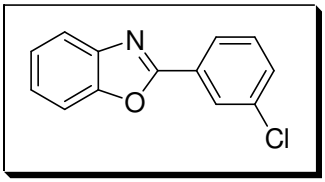
Mp: 63-64 ˚C (lit.[6g] 63-65 ˚C)

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.17 (d, J = 7.6 Hz, 1H), 7.80-7.78 (m, 1H), 7.59-7.56 (m, 1H), 7.40-7.31 (m, 5H), 2.80 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 163.4, 150.3, 142.2, 138.9, 131.9, 130.9, 130.0, 126.3, 126.1, 125.1, 124.4, 120.2, 110.5, 22.4.

FT-IR (KBr): 2950, 1614, 1547, 1485, 1451, 1262, 1240, 1205, 1145, 1108, 1028, 920 cm^{-1}.

Anal. Calcd. for $C_{14}H_{11}NO$: C, 80.36; H, 5.30; N, 6.69. Found: C, 80.41; H, 5.28; N, 6.65.



2-(3-Chlorophenyl)benzoxazole[6j] **(2c)**: 3-Chlorobenzamide (156 mg, 1.0 mmol), 2-bromoiodobenzene (283 mg, 1.0 mmol), CuI (19 mg, 10 mol %), KOH (140 mg, 2.5 mmol) and TBAB (645 mg, 2.0 mmol) were subjected to the reaction conditions described in the general procedure to afford the title compound as white solid in 57% (131 mg) yield.

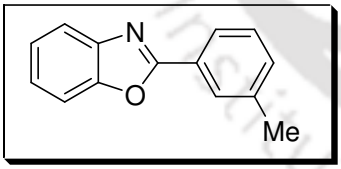
Mp: 122-123 ˚C (lit.[6j] 122 ˚C)

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.24 (t, *J* = 2.0 Hz, 1H), 8.14-8.11 (m, 1H), 7.78-7.75 (m, 1H), 7.59-7.56 (m, 1H), 7.50-7.42 (m, 2H), 7.38-7.35 (m, 2H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 161.8, 151.0, 142.1, 135.3, 131.6, 130.4, 129.1, 127.8, 125.8, 125.7, 125.0, 120.4, 110.9.

FT-IR (KBr): 2961, 1638, 1616, 1549, 1465, 1452, 1433, 1261, 1240, 1073, 1049, 928 cm^{-1}.

Anal. Calcd. for $C_{13}H_8ClNO$: C, 67.99; H, 3.51; N, 6.10. Found: C, 68.06; H, 3.48; N, 6.14.



2-(3-Methylphenyl)benzoxazole[7a] **(2d)**: 3-Methylbenzamide (135 mg, 1.0 mmol), 2-bromoiodobenzene (283 mg, 1.0 mmol), CuI (19 mg, 10 mol %), KOH (140 mg, 2.5 mmol) and TBAB (645 mg, 2.0 mmol) were subjected to the reaction conditions described in the general procedure to afford the title compound as light yellow solid in 67% (140 mg) yield.

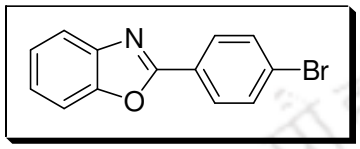
Mp: 80-81 ˚C (lit.[7a] 79-80 ˚C).

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.09 (s, 1H), 8.05 (d, *J* = 7.6 Hz, 1H), 7.77-7.74 (m, 1H), 7.58-7.56 (m, 1H), 7.40 (t, *J* = 8.0 Hz, 1H), 7.36-7.31 (m, 3H), 2.44 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 163.4, 150.9, 142.3, 138.9, 132.5, 129.0, 128.3, 127.2, 125.2, 124.9, 124.7, 120.1, 110.7, 21.5.

FT-IR (KBr): 2962, 1718, 1618, 1552, 1487, 1453, 1261, 1245, 1093, 1020, 919 cm^{-1}.

Anal. Calcd. for $C_{14}H_{11}NO$: C, 80.36; H, 5.30; N, 6.69. Found: C, 80.43; H, 5.32; N, 6.73.



2-(4-Bromophenyl)benzoxazole[6b] **(2e)**: 4-Bromobenzamide (200 mg, 1.0 mmol), 2-bromoiodobenzene (283 mg, 1.0 mmol), CuI (19 mg, 10 mol %), KOH (140 mg, 2.5 mmol) and TBAB (645 mg, 2.0 mmol) were subjected to the reaction conditions described in the general procedure to afford the title compound as white solid in 55% (151 mg) yield.

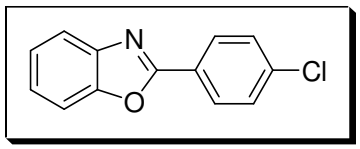
Mp: 156-157 ˚C (lit.[6b] 157-158 ˚C)

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.12-8.09 (m, 2H), 7.76-7.74 (m, 1H), 7.67-7.64 (m, 2H), 7.57-7.55 (m, 1H), 7.36-7.34 (m, 2H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 162.3, 150.9, 142.2, 132.4, 129.2, 126.4, 126.3, 125.6, 124.9, 120.3, 110.8.

FT-IR (KBr): 2924, 1615, 1592, 1547, 1484, 1452, 1400, 1342, 1294, 1261, 1244, 1176, 1107, 1069, 1052, 1009 cm^{-1}.

Anal. Calcd. for $C_{13}H_8BrNO$: C, 56.96; H, 2.94; N, 5.11. Found: C, 56.90; H, 2.91; N, 5.07.



2-(4-Chlorophenyl)benzoxazole[6g] **(2f)**: 4-Chlorobenzamide (156 mg, 1.0 mmol), 2-bromoiodobenzene (283 mg, 1.0 mmol), CuI (19 mg, 10 mol %), KOH (140 mg, 2.5 mmol) and TBAB (645 mg, 2.0 mmol) were subjected to the reaction conditions described in the general procedure to afford the title compound as white solid in 53% (122 mg) yield.

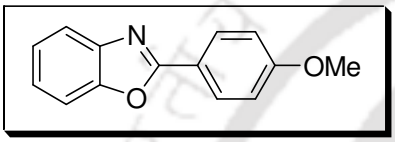
Mp: 151-152 ˚C (lit.[6g] 152-153 ˚C).

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.19-8.16 (m, 2H), 7.76-7.74 (m, 1H), 7.57-7.55 (m, 1H), 7.50-7.47 (m, 2H), 7.37-7.34 (m, 2H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 162.1, 150.8, 142.1, 137.8, 129.3, 128.9, 125.7, 125.4, 124.8, 120.2, 110.7.

FT-IR (KBr): 1635, 1617, 1484, 1452, 1405, 1244, 1091, 1055, 1011, 925 cm^{-1}.

Anal. Calcd. for $C_{13}H_8ClNO$: C, 67.99; H, 3.51; N, 6.10. Found: C, 67.94; H, 3.53; N, 6.06.



2-(4-Methoxyphenyl)benzoxazole[6b] **(2g)**: 4-Methoxybenzamide (151 mg, 1.0 mmol), 2-bromoiodobenzene (283 mg, 1.0 mmol), CuI (19 mg, 10 mol %), KOH (140 mg, 2.5 mmol) and TBAB (645 mg, 2.0 mmol) were subjected to the reaction conditions described in the general procedure to afford the title compound as white solid in 65% (146 mg) yield.

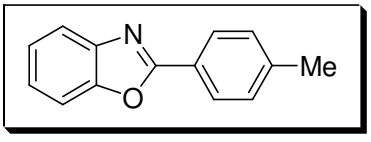
Mp: 97-98 ˚C (lit.[6b] 97-98 ˚C).

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.19 (dd, *J* = 1.6, 6.8 Hz, 2H), 7.73-7.71 (m, 1H), 7.55-7.52 (m, 1H), 7.32-7.29 (m, 2H), 7.02 (dd, *J* = 2.0, 6.8 Hz, 2H), 3.87 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 163.3, 162.4, 150.8, 142.4, 129.5, 124.7, 124.5, 119.8, 119.7, 114.5, 110.5, 55.5.

FT-IR (KBr): 2958, 2924, 2853, 1618, 1605, 1504, 1471, 1454, 1421, 1257, 1243, 1188, 1169, 1019 cm^{-1}.

Anal. Calcd. for $C_{14}H_{11}NO_2$: C, 74.65; H, 4.92; N, 6.22. Found: C, 74.72; H, 4.94; N, 6.18.



2-(4-Methylphenyl)benzoxazole[6h] **(2h)**: 4-Methylbenzamide (135 mg, 1.0 mmol), 2-bromoiodobenzene (283 mg, 1.0 mmol), CuI (19 mg, 10 mol %), KOH (140 mg, 2.5 mmol) and TBAB (645 mg, 2.0 mmol) were subjected to the reaction conditions described in the general procedure to afford the title compound as white solid in 60% (126 mg) yield.

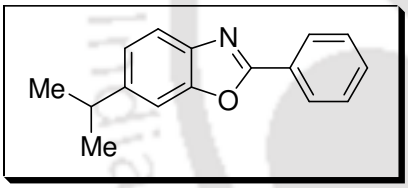
Mp: 115-116 ˚C (lit.[6h] 116 ˚C).

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.14(dd, *J* = 2.0, 6.8 Hz, 2H), 7.75-7.73 (m, 1H), 7.57-7.54 (m, 1H), 7.34-7.30 (m, 4H), 2.42 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 163.5, 150.9, 142.4, 142.2, 129.8, 127.8, 125.0, 124.7, 124.6, 120.0, 110.7, 21.8.

FT-IR (KBr): 2961, 2917, 1635, 1622, 1500, 1450, 1407, 1259, 1243, 1172, 1108, 1054, 1015 cm^{-1}.

Anal. Calcd. for $C_{14}H_{11}NO$: C, 80.36; H, 5.30; N, 6.69. Found: C, 80.32; H, 5.33; N, 6.64.



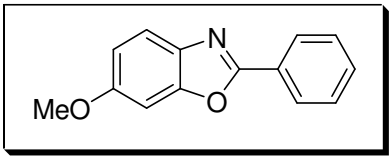
6-Isopropyl-2-phenylbenzoxazole (2i): Benzamide (121 mg, 1.0 mmol), 2-bromo-4-isopropileiodobenzene (325 mg, 1.0 mmol), CuI (19 mg, 10 mol %), KOH (140 mg, 2.5 mmol) and TBAB (645 mg, 2.0 mmol) were subjected to the reaction conditions described in the general procedure to afford the title compound as light yellow oil in 68% (159 mg) yield.

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.24-8.20 (m, 2H), 7.67 (d, *J* = 8.0 Hz 1H), 7.54-7.47 (m, 3H), 7.44 (d, *J* = 1.6 Hz, 1H), 7.23 (dd, *J* = 1.6, 8.0 Hz, 1H), 3.08-3.01 (m, 1H), 1.32 (d, *J* = 6.8 Hz, 6H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 162.8, 151.2, 147.1, 140.3, 131.4, 129.0, 127.6, 123.6, 119.6, 108.2, 34.6, 24.5.

FT-IR (neat): 2962, 1622, 1555, 1484, 1450, 1432, 1323, 1260, 1096, 1052, 1024, 923 cm^{-1}.

Anal. Calcd. for $C_{16}H_{15}NO$: C, 80.98; H, 6.37; N, 5.90. Found: C, 81.06; H, 6.39; N, 5.86.



6-Methoxy-2-phenylbenzoxazole[7b] **(2j)**: Benzamide (121 mg, 1.0 mmol), 2-bromo-4-methoxyiodobenzene (313 mg, 1.0 mmol), CuI (19 mg, 10 mol %), KOH (140 mg, 2.5 mmol) and TBAB (645 mg, 2.0 mmol) were subjected to the reaction conditions described in the general procedure to afford the title compound as grey solid in 43% (97 mg) yield.

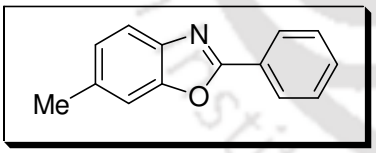
Mp: 76-77˚C (lit.[7b] 75-76 ˚C).

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.20-8.17 (m, 2H), 7.63 (d, *J* = 8.8 Hz, 1H), 7.50-7.48 (m, 3H), 7.10 (d, *J* = 2.4 Hz, 1H), 6.96 (dd, *J* = 2.4, 8.8 Hz, 1H), 3.87 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 162.4, 158.5, 151.8, 136.1, 131.2, 129.0, 127.5, 127.4, 120.2, 113.0, 95.6, 56.1.

FT-IR (KBr): 2961, 1619, 1555, 1487, 1449, 1433, 1347, 1321, 1144, 1128, 1097, 1052, 1022, 920 cm^{-1}.

Anal. Calcd. for $C_{14}H_{11}NO_2$: C, 74.65; H, 4.92; N, 6.22. Found: C, 74.70; H, 4.90; N, 6.25.



6-Methyl-2-phenylbenzoxazole[6h] **(2k)**: Benzamide (121 mg, 1.0 mmol), 2-bromo-4-methyliodobenzene (297 mg, 1.0 mmol), CuI (19 mg, 10 mol %), KOH (140 mg, 2.5 mmol) and TBAB (645 mg, 2.0 mmol) were subjected to the reaction conditions described in the general procedure to afford the title compound as white solid in 56% (117 mg) yield.

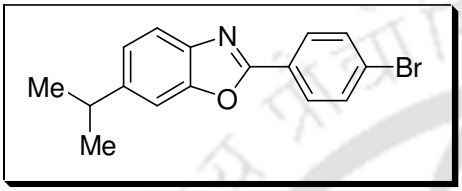
Mp: 92-93 ˚C (lit.[6h] 93 ˚C).

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.23-8.21 (m, 2H), 7.63 (d, *J* = 8.0 Hz, 1H), 7.52-7.49 (m, 3H), 7.37 (d, *J* = 0.8 Hz, 1H), 7.16 (d, *J* = 7.6 Hz, 1H), 2.49 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 162.7, 151.2, 140.1, 135.7, 131.4, 129.0, 127.6, 125.9, 119.5, 110.9, 21.9.

FT-IR (KBr): 3054, 2961, 2917, 2857, 1626, 1615, 1552, 1476, 1448, 1336, 1261, 1097, 1072, 1050, 1020 cm^{-1}.

Anal. Calcd. for $C_{14}H_{11}NO$: C, 80.36; H, 5.30; N, 6.69. Found: C, 80.30; H, 5.27; N, 6.74.



6-Isopropyl-2-(4-bromophenyl)benzoxazole (2l): 4-Bromobenzamide (200 mg, 1.0 mmol), 2-bromo-4-isopropileiodobenzene (325 mg, 1.0 mmol), CuI (19 mg, 10 mol %), KOH (140 mg, 2.5 mmol) and TBAB (645 mg, 2.0 mmol) were subjected to the reaction conditions described in the general procedure to afford the title compound as grey solid in 56% (177 mg) yield.

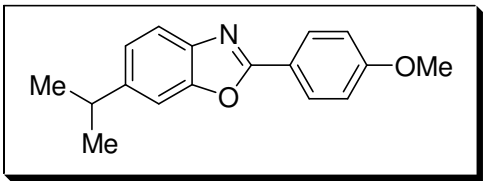
Mp: 101-102 ˚C.

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.09-8.06 (m, 2H), 7.66-7.62 (m, 3H), 7.42 (t, J = 0.8 Hz, 1H), 7.24-7.21 (m, 1H), 3.06-3.01 (m, 1H), 1.31 (d, J = 7.2 Hz, 6H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 162.0, 151.3, 147.5, 140.3, 132.4, 129.0, 126.5, 126.1, 123.9, 119.7, 108.3, 34.7, 24.5.

FT-IR (KBr): 2960, 2923, 2868, 1721, 1635, 1614, 1591, 1546, 1479, 1432, 1397, 1261, 1102, 1067, 1045 cm^{-1}.

Anal. Calcd. for $C_{16}H_{14}BrNO$: C, 60.78; H, 4.46; N, 4.43. Found: C, 60.83; H, 4.48; N, 4.40.



6-Isopropyl-2-(4-methoxyphenyl)benzoxazole (2m): 4-Methoxybenzamide (151 mg, 1.0 mmol), 2-bromo-4-isopropileiodobenzene (325 mg, 1.0 mmol), CuI (19 mg, 10 mol %),

KOH (140 mg, 2.5 mmol) and TBAB (645 mg, 2.0 mmol) were subjected to the reaction conditions described in the general procedure to afford the title compound as light yellow solid in 62% (166 mg) yield.

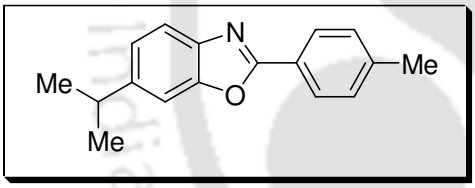
Mp: 47-48 ˚C.

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.17 (dd, *J* = 1.6, 6.8 Hz, 2H), 7.62 (d, *J* = 8.4 Hz, 1H), 7.40 (d, *J* = 1.2 Hz, 1H), 7.20 (dd, *J* = 1.6, 8.4 Hz, 1H), 7.01 (dd, *J* = 2.0, 6.8 Hz, 2H), 3.87 (s, 3H), 3.07-3.00 (m, 1H), 1.31 (d, *J* = 6.8 Hz, 6H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 162.9, 162.3, 151.1, 146.5, 140.5, 129.3, 123.4, 120.1, 119.2, 114.4, 108.0, 55.4, 34.5, 24.5.

FT-IR (KBr): 2956, 1618, 1579, 1557, 1455, 1434, 1420, 1382, 1363, 1318, 1305, 1251, 1183, 1170, 1128, 1116, 1061, 1051, 1029, 937, 920 cm^{-1}.

Anal. Calcd. for $C_{17}H_{17}NO_2$: C, 76.38; H, 6.41; N, 5.24. Found: C, 76.44; H, 6.38; N, 5.28.



6-Isopropyl-2-(4-methylphenyl)benzoxazole (2n): 4-Methylbenzamide (135 mg, 1.0 mmol), 2-bromo-4-isopropileiodobenzene (325 mg, 1.0 mmol), CuI (19 mg, 10 mol %), KOH (140 mg, 2.5 mmol) and TBAB (645 mg, 2.0 mmol) were subjected to the reaction conditions described in the general procedure to afford the title compound as light yellow solid in 71% (178 mg) yield.

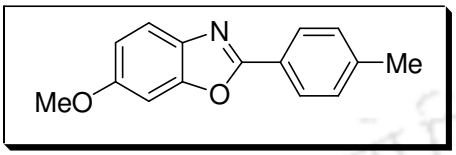
Mp: 51-52 ˚C.

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.12-8.09 (m, 2H), 7.65 (d, *J* = 7.6 Hz, 1H), 7.42 (t, *J* = 0.8 Hz, 1H), 7.31 (d, *J* = 8.0 Hz, 2H), 7.22 (dd, *J* = 1.6, 8.0 Hz, 1H), 3.08-3.01 (m, 1H), 2.42 (s, 3H), 1.31 (d, *J* = 7.2 Hz, 6H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 163.1, 151.2, 146.8, 141.9, 140.4, 129.7, 127.5, 124.8, 123.5, 119.4, 108.1, 34.6, 24.5, 21.7.

FT-IR (KBr): 2947, 1619, 1499, 1482, 1431, 1320, 1258, 1179, 1094, 1050, 1014, 938, 922 cm^{-1}.

Anal. Calcd. for $C_{17}H_{17}NO$: C, 81.24; H, 6.82; N, 5.57. Found: C, 81.31; H, 6.84; N, 5.52.



6-Methoxy-2-(4-methylphenyl)benzoxazole (2o): 4-Methylbenzamide (135 mg, 1.0 mmol), 2-bromo-4-methoxyiodobenzene (313 mg, 1.0 mmol), CuI (19 mg, 10 mol %), KOH (140 mg, 2.5 mmol) and TBAB (645 mg, 2.0 mmol) were subjected to the reaction conditions described in the general procedure to afford the title compound as grey solid in 49% (117 mg) yield.

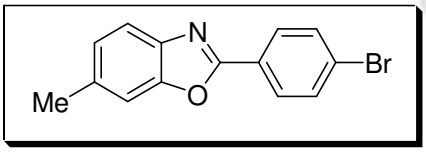
Mp: 83-84 ˚C.

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.08 (d, *J* = 8.4 Hz, 2H), 7.61 (d, *J* = 8.8 Hz, 1H), 7.30 (d, *J* = 8.0 Hz, 2H), 7.09 (d, *J* = 2.4 Hz, 1H), 6.94 (dd, *J* = 2.4, 8.4 Hz, 1H), 3.86 (s, 3H), 2.41 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 162.7, 158.3, 151.7, 141.7, 136.1, 129.8, 127.4, 124.8, 120.0, 112.8, 95.6, 56.1, 21.8.

FT-IR (KBr): 2961, 1627, 1503, 1487, 1462, 1410, 1433, 1347, 1261, 1214, 1143, 1126, 1096, 1019 cm^{-1}.

Anal. Calcd. for $C_{15}H_{13}NO_2$: C, 75.30; H, 5.48; N, 5.85. Found: C, 75.25; H, 5.45; N, 5.82.



6-Methyl-2-(4-bromophenyl)benzoxazole (2p): 4-Bromobenzamide (200 mg, 1.0 mmol), 2-bromo-4-methyliodobenzene (297 mg, 1.0 mmol), CuI (19 mg, 10 mol %), KOH (140 mg, 2.5 mmol) and TBAB (645 mg, 2.0 mmol) were subjected to the reaction

conditions described in the general procedure to afford the title compound as white solid in 50% (144 mg) yield.

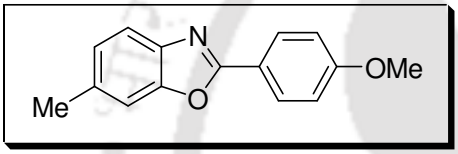
Mp: 157-158 ˚C.

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.08-8.05 (m, 2H), 7.64-7.60 (m, 3H), 7.35 (s, 1H), 7.17 (d, *J* = 8.0 Hz, 1H), 2.49 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 161.8, 151.2, 140.0, 136.1, 132.3, 129.0, 126.4, 126.2, 119.6, 111.0, 22.0.

FT-IR (KBr): 1636, 1478, 1396, 1261, 1245, 1147, 1097, 1049, 1005 cm^{-1}.

Anal. Calcd. for $C_{14}H_{10}BrNO$: C, 58.36; H, 3.50; N, 4.86. Found: C, 58.31; H, 3.48; N, 4.81.



6-Methyl-2-(4-methoxyphenyl)benzoxazole[7c] **(2q)**: 4-Methoxybenzamide (151 mg, 1.0 mmol), 2-bromo-4-methyliodobenzene (297 mg, 1.0 mmol), CuI (19 mg, 10 mol %), KOH (140 mg, 2.5 mmol) and TBAB (645 mg, 2.0 mmol) were subjected to the reaction conditions described in the general procedure to afford the title compound as yellow solid in 63% (151 mg) yield.

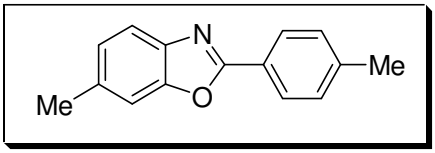
Mp: 91-92 ˚C (lit.[7c] 90-91˚C).

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.16 (dd, *J* = 2.0, 6.8 Hz, 2H), 7.59 (d, *J* = 8.0 Hz, 1H), 7.34 (d, *J* = 0.8 Hz, 1H), 7.13 (d, *J* = 8.0 Hz, 1H), 7.01 (dd, *J* = 2.0, 6.8 Hz, 2H), 3.87 (s, 3H), 2.48 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 162.9, 162.3, 151.1, 140.2, 135.2, 129.4, 125.8, 120.1, 119.1, 114.5, 110.8, 55.6, 21.9.

FT-IR (KBr): 2918, 1619, 1604, 1504, 1457, 1437, 1420, 1336, 1321, 1305, 1288, 1260, 1248, 1185, 1176, 1121, 1059, 1024, 941, 920 cm^{-1}.

Anal. Calcd. for $C_{15}H_{13}NO_2$: C, 75.30; H, 5.48; N, 5.85. Found: C, 75.34; H, 5.50; N, 5.88.



6-Methyl-2-(4-methylphenyl)benzoxazole[7c] **(2r)**: 4-Methylbenzamide (135 mg, 1.0 mmol), 2-bromo-4-methyliodobenzene (297 mg, 1.0 mmol), CuI (19 mg, 10 mol %), KOH (140 mg, 2.5 mmol) and TBAB (645 mg, 2.0 mmol) were subjected to the reaction conditions described in the general procedure to afford the title compound as light yellow solid in 65% (145 mg) yield.

Mp: 102-103 ˚C (lit.[7c] 103-104 ˚C).

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.11 (d, *J* = 8.0 Hz, 2H), 7.61 (d, *J* = 8.4 Hz, 1H), 7.35 (s, 1H), 7.31 (d, *J* = 8.0 Hz, 2H), 7.14 (d, *J* = 8.0 Hz, 1H), 2.48 (s, 3H), 2.41 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 163.0, 151.1, 141.9, 140.1, 135.4, 129.8, 127.6, 125.8, 124.7, 119.3, 110.8, 22.0, 21.8.

FT-IR (KBr): 3050, 2924, 1619, 1555, 1500, 1479, 1408, 1335, 1250, 1173, 1116, 1053, 1015, 940, 925 cm^{-1}.

Anal. Calcd. for $C_{15}H_{13}NO$: C, 80.69; H, 5.87; N, 6.27. Found: C, 80.75; H, 5.89; N, 6.30.

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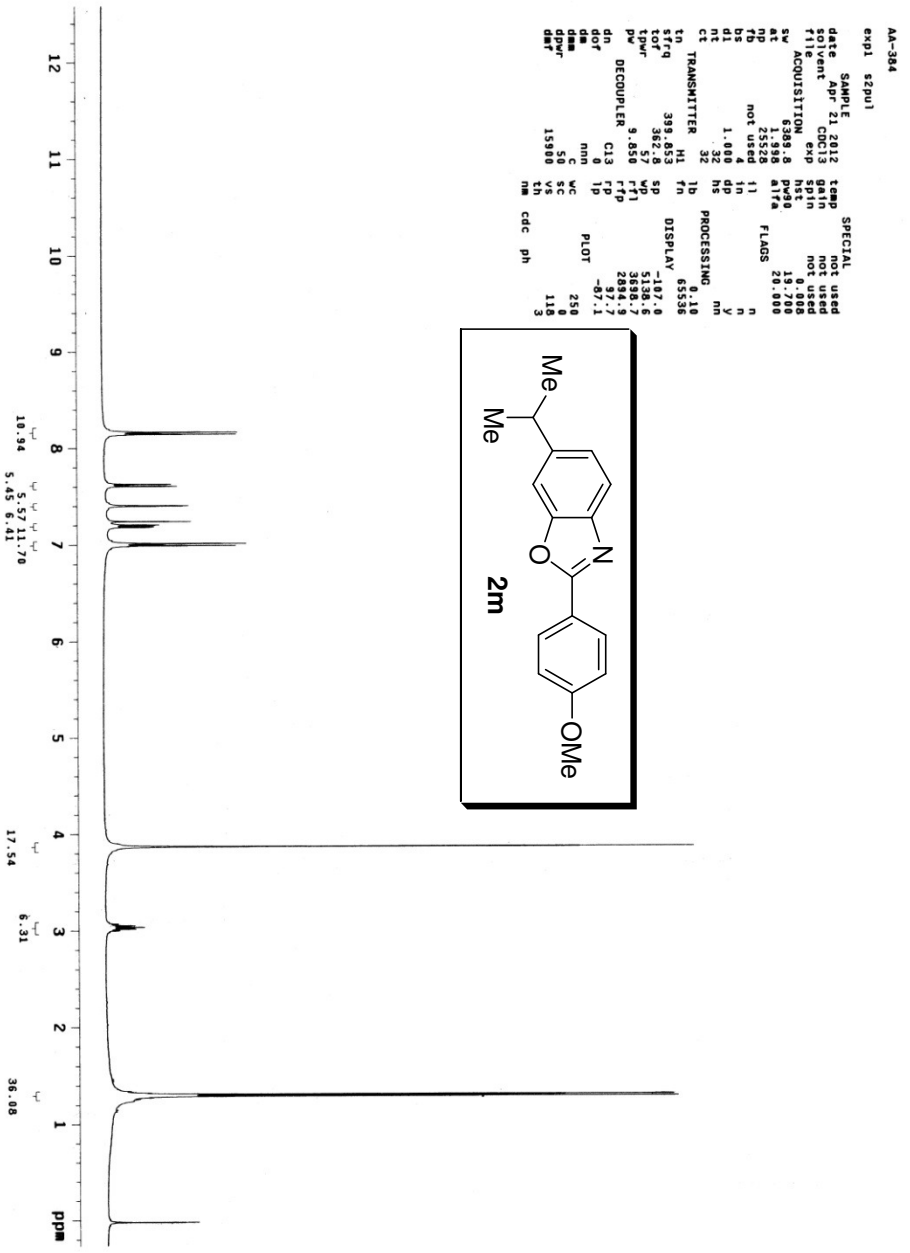
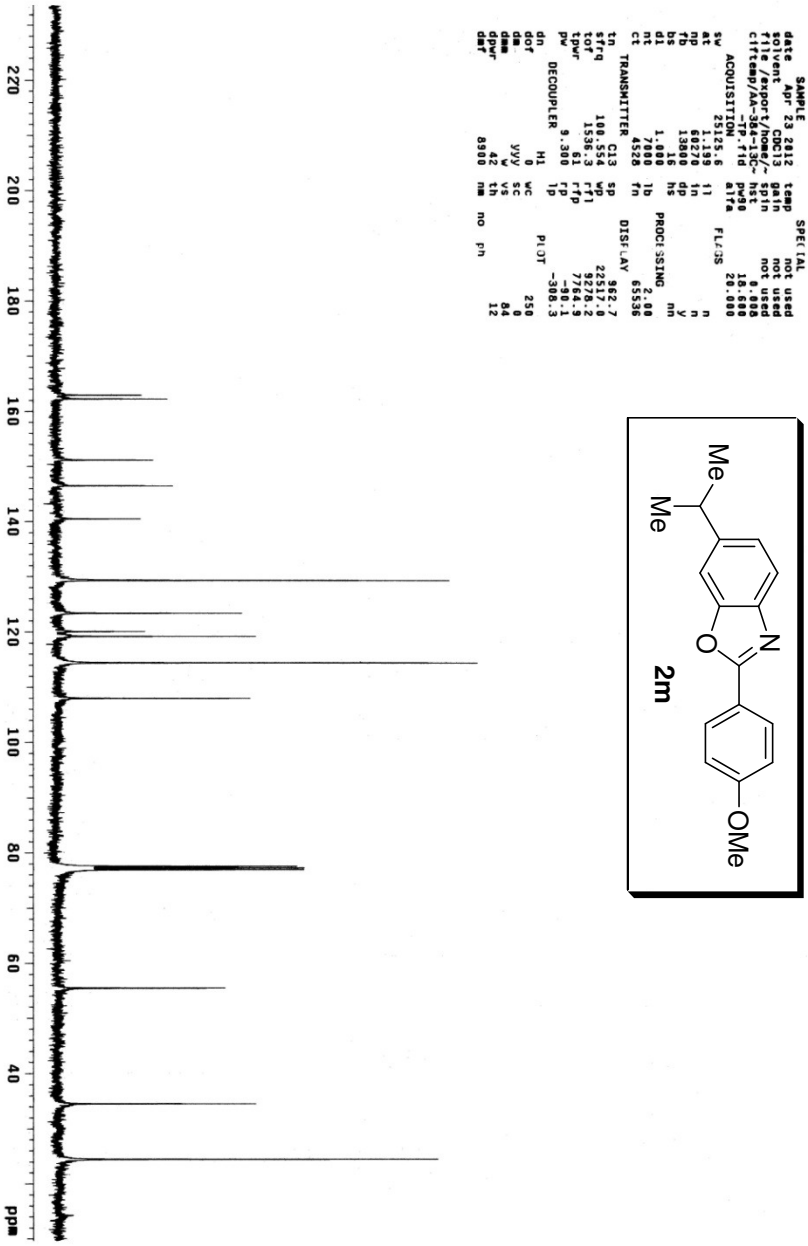
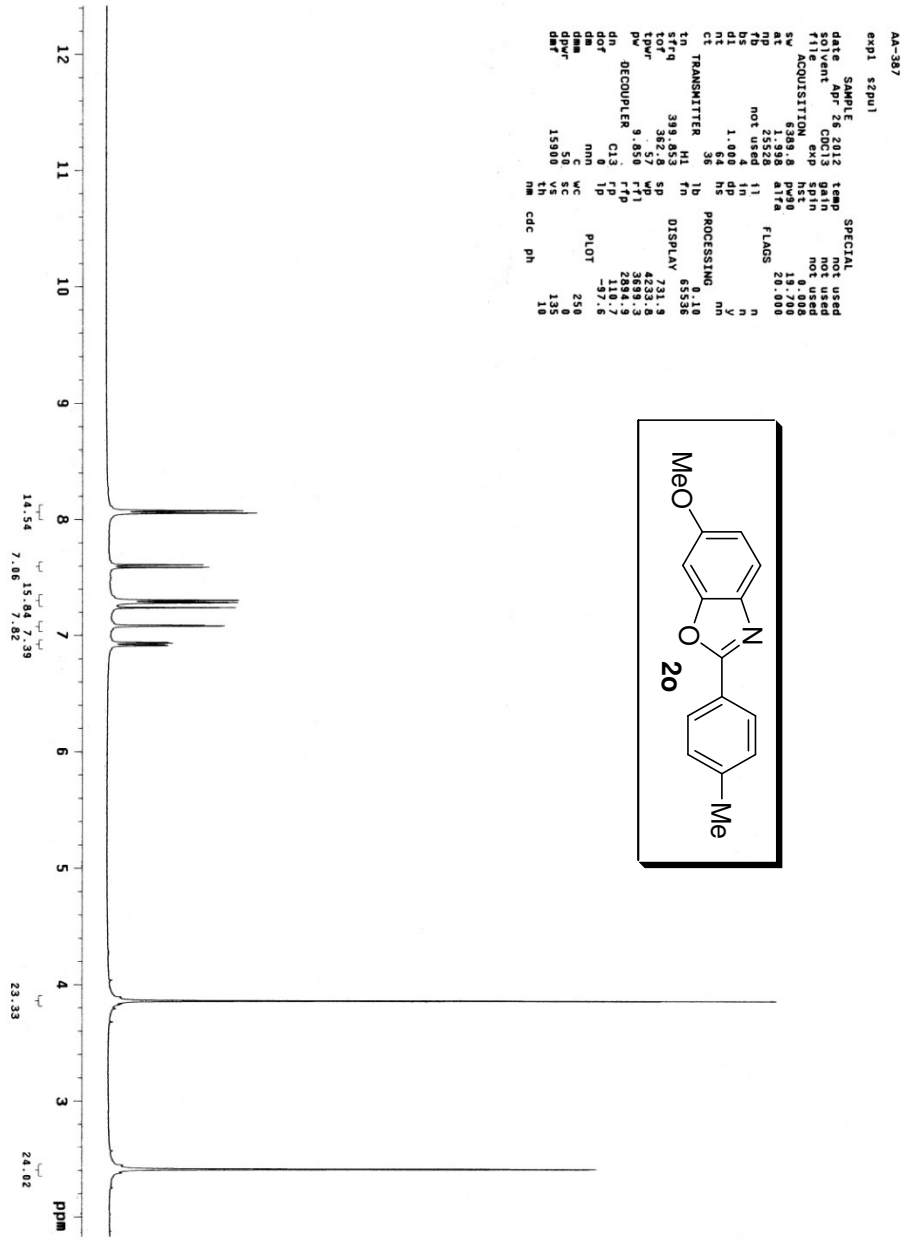
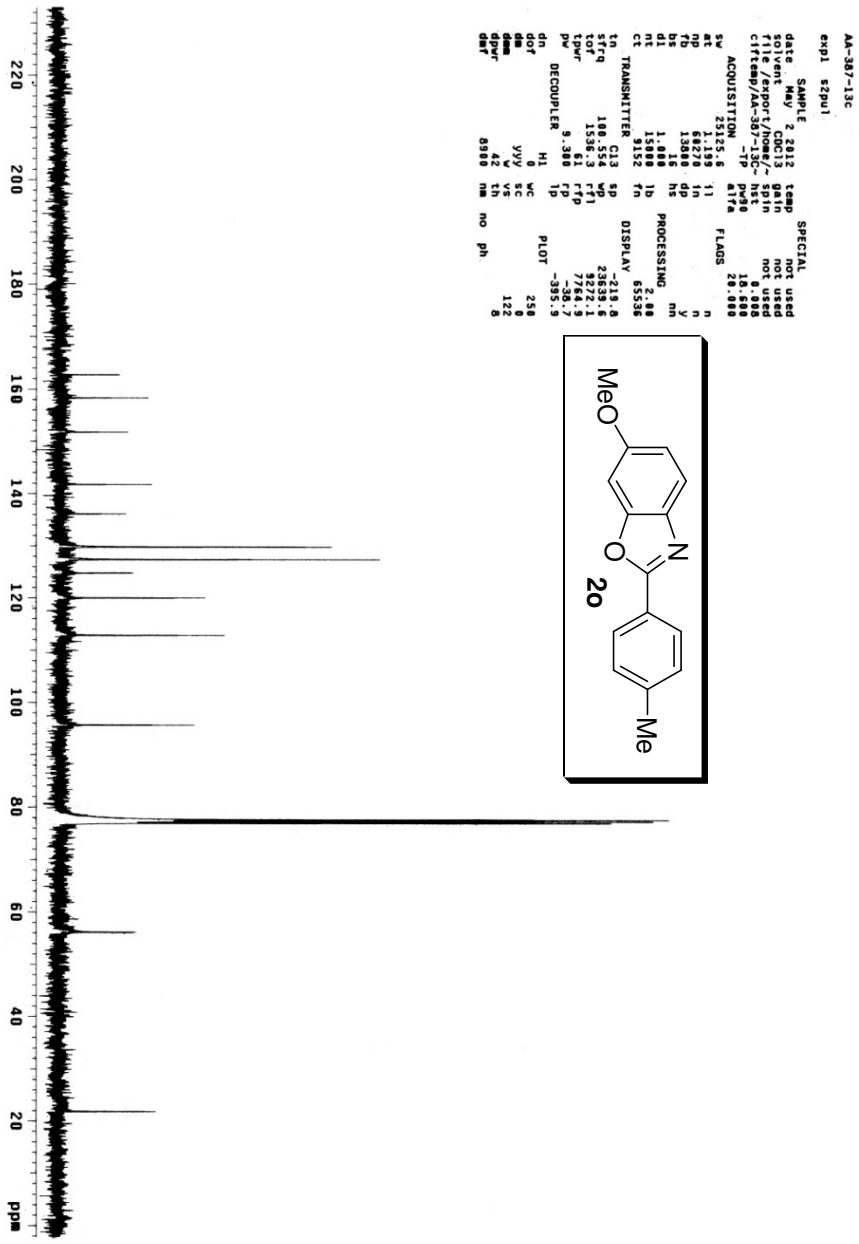
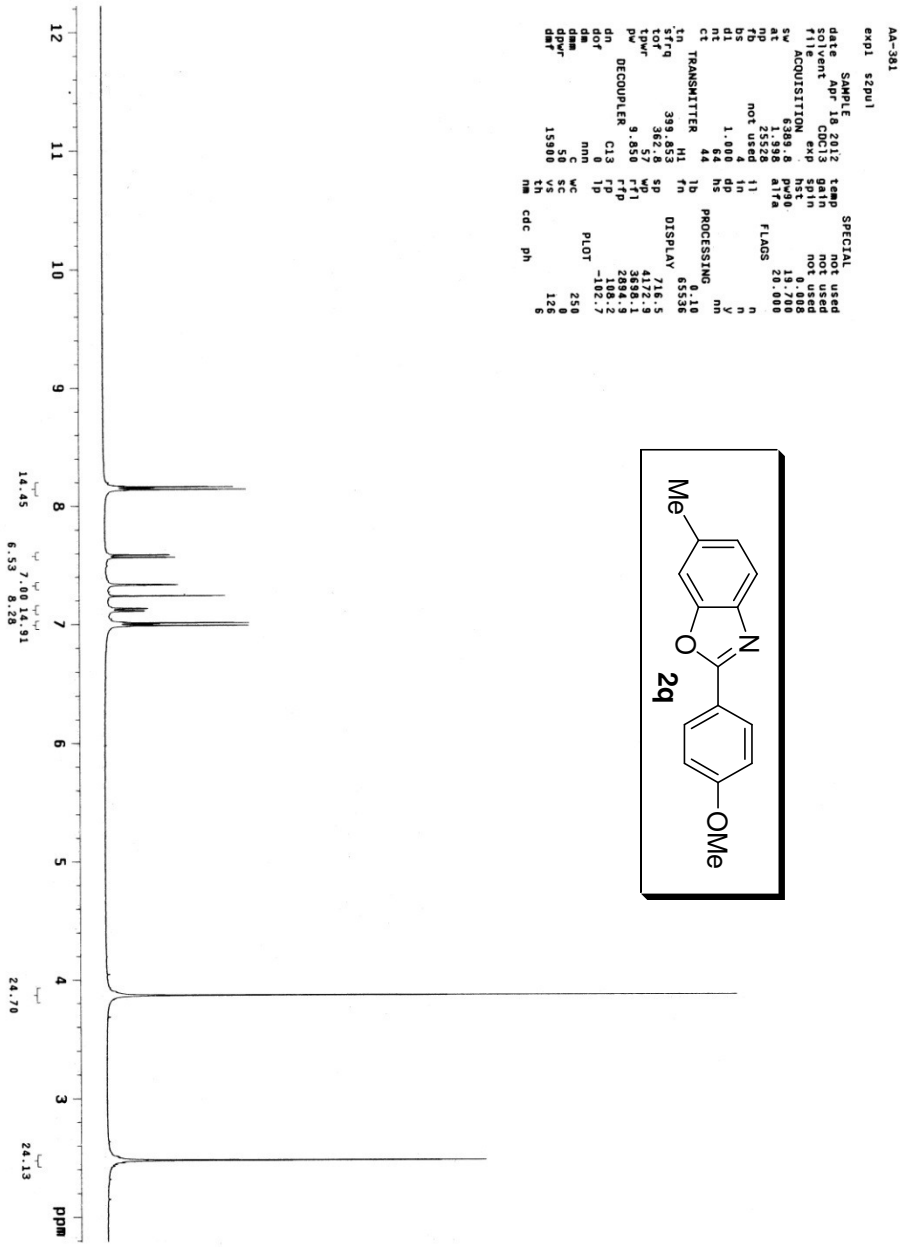
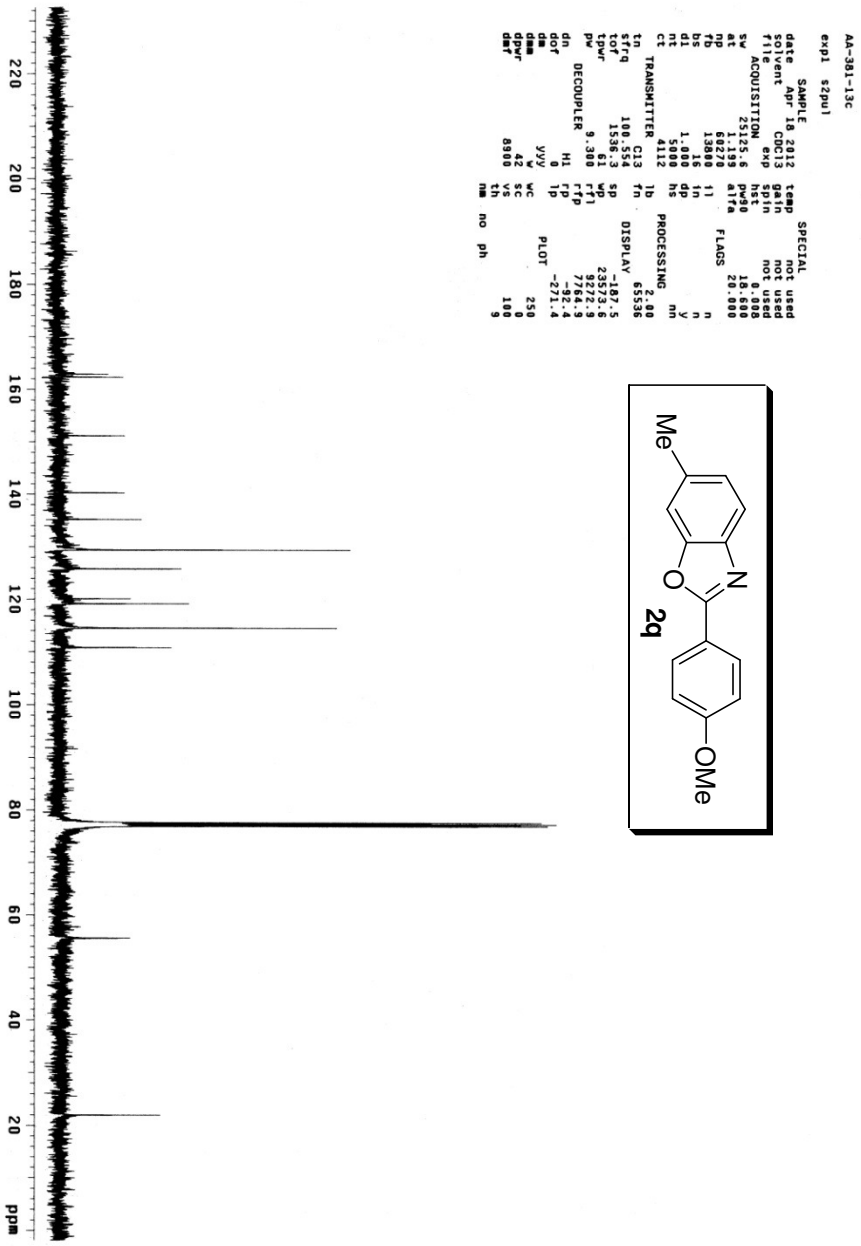












Chapter III

Domino Cu_2O-Catalyzed Synthesis of Polysubstituted Indoles

Indoles are probably the most common heterocycles found in nature[1] and have been referred to as 'privileged structures' of medicinal importance due to their high binding affinity with many receptors (Figure 1).[2] Indoles are also known as important structural constituent for the development of agrochemicals,[3a] materials[3b-c] and perfumes.[3d] Over a hundred years, the synthesis and functionalization of indoles has been a major area of focus for the synthetic organic chemists and numerous methods have been developed for their preparation.[4] However, in some cases, specific substitution patterns remain difficult to obtain by standard indole forming reactions so the search for new simple, general and especially regioselective synthetic methods for the construction of substituted indole scaffold continues to be of tremendous interest in organic synthesis.

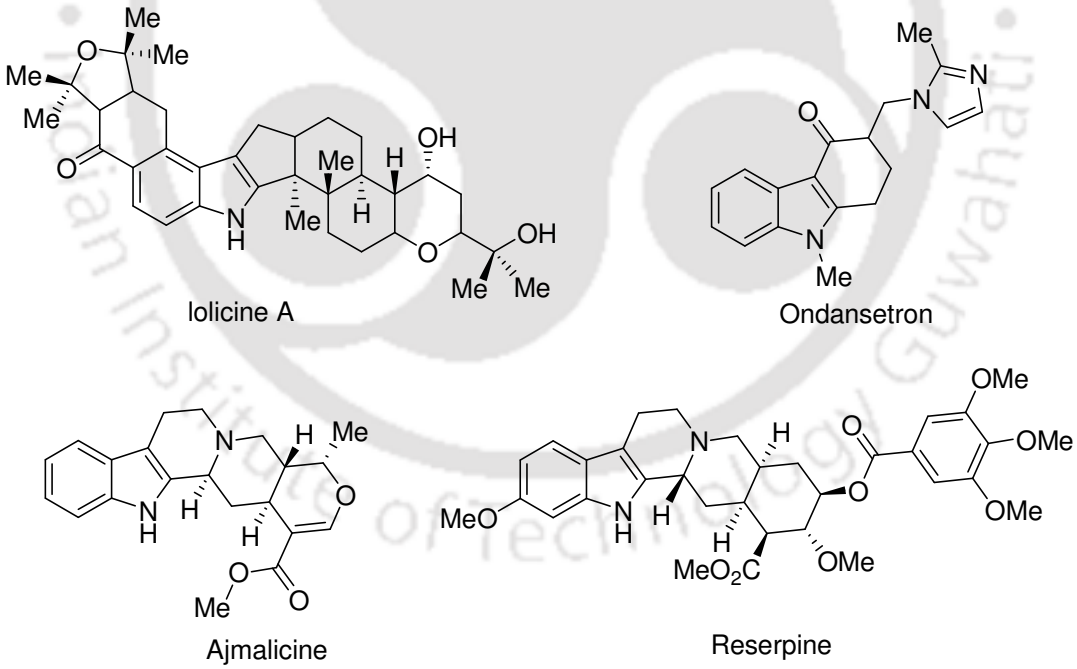
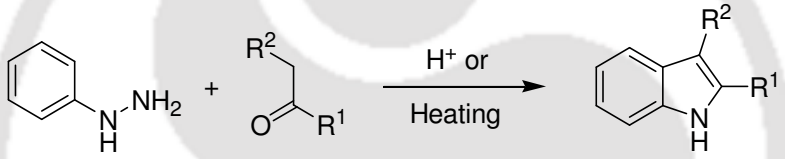


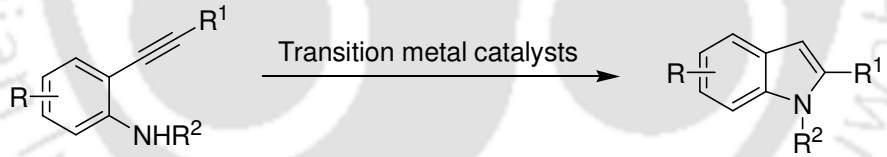
Figure 1 Example of Biologically Active and Naturally Occurring Compounds.

The traditional method for the construction of indole moieties is century-old and widely used Fischer indole synthesis. The protocol involves condensation of hydrazines

and aldehyde or ketone followed by acid-catalyzed or thermal sigmatropic rearrangement to provide indole skeleton (Scheme 1).[5] However, the use of strong acidic condition limits the functional group tolerance for a wide range of substrates. Some of these drawbacks were overcome by transition metal such as palladium,[6a-b] copper,[6c-d] zinc[6e-f] and gold[6g] catalyzed cyclization of 2-alkynylanilines or 2-alkynylanilides to get the indole skeleton (Scheme 2). But the requirements of prefunctionalized precursors reduce the chance for a wide range of application of these methods. In recent years, the development of sustainable cross-coupling methods using transition-metal catalysts, particularly palladium[7] and copper[8] catalysts, and *C-H* functionalization *C-C/C-N* bond formation methods[9] have been facilitating to construct the target indole heterocycles with broad substrates scope and comparatively under milder reaction conditions.



Scheme 1



Scheme 2

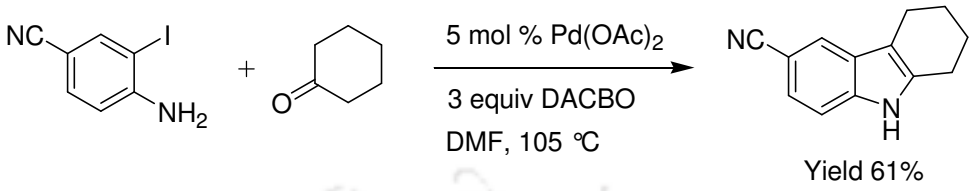
3.1 Cross-Coupling Methods

Palladium- and copper-catalyzed cross-coupling methods have been used for the construction of indole skeletons.

3.1.1 Palladium Catalysts

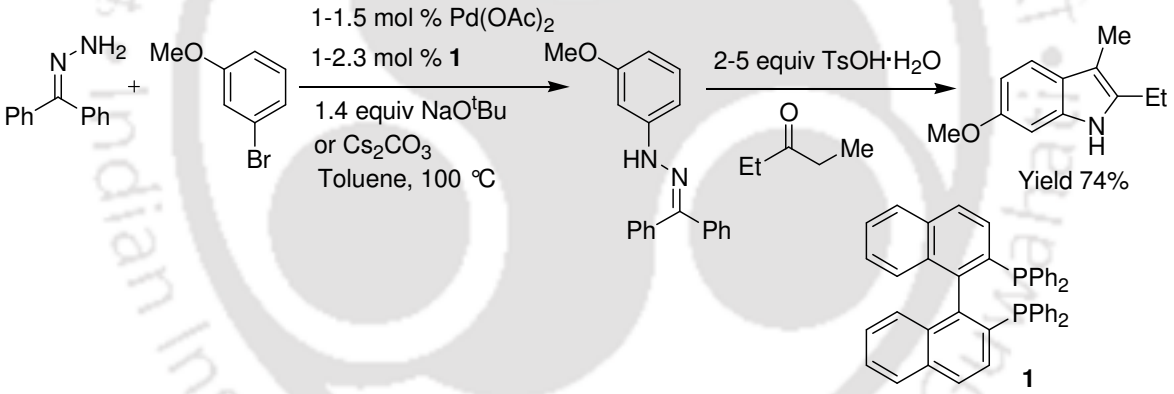
Chen and co-workers have used a straightforward protocol for the synthesis of indole skeleton by condensation of *o*-iodoaniline with ketone followed by palladium catalyzed

intramolecular Heck reaction. The use of an amine base such as DABCO and DMF as a solvent is crucial for the successful completion of this reaction (Scheme 3).[7a]



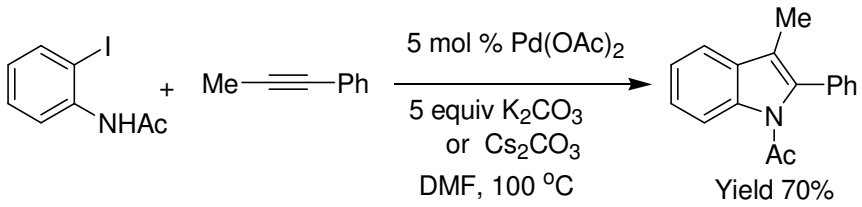
Scheme 3

Buchwald and co-workers have used palladium-catalyzed carbon-nitrogen cross-coupling strategy for the synthesis of indole skeleton. Commercially available benzophenone hydrazone is cross-coupled with aryl bromides followed by acid catalyzed sigmatropic rearrangement to give the desired indole (Scheme 4).[7b]



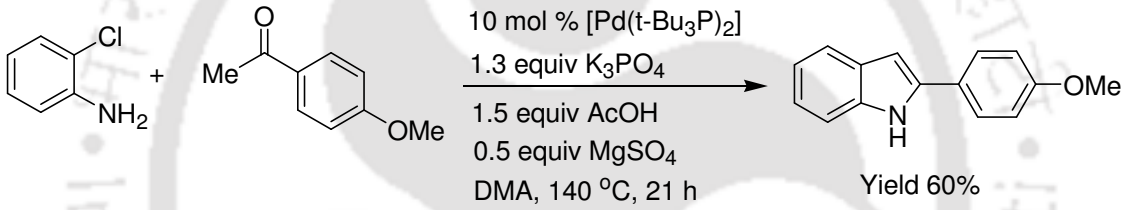
Scheme 4

Palladium catalyzed coupling of *o*-iodoaniline and its derivatives with various alkyne have been successfully used by Larock and co-workers to synthesize regioselectively 2,3-disubstituted indoles.[7c] The smaller substituent goes to the 3-position and the bulky substituent goes to the 2-position i.e. next to the nitrogen atom of indole skeleton (Scheme 5).



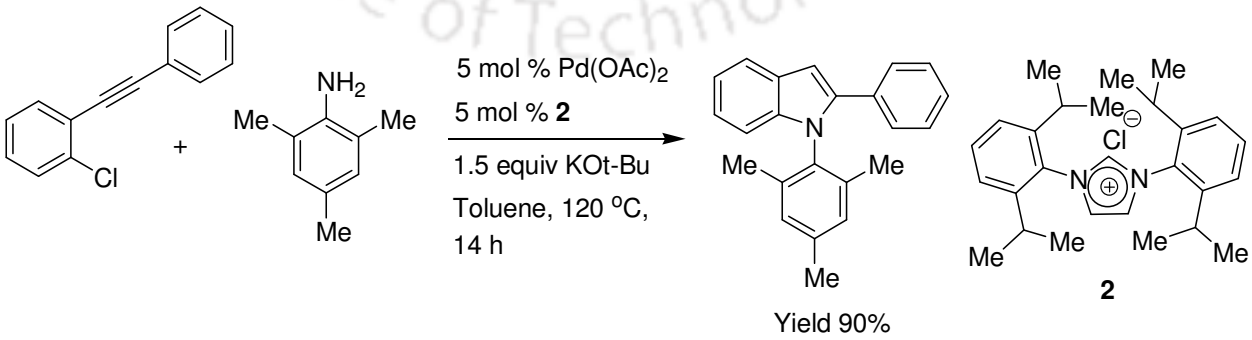
Scheme 5

The synthesis of polyfunctionalized indoles by direct reaction of substituted 2-chloroanilines with cyclic or acyclic ketones was discovered by Nazare and co-workers in the presence of palladium catalyst (Scheme 6).[7d] The reaction involves the use of K_3PO_4 along with acetic acid and magnesium sulfate as an additive in dimethylacetamide (DMA).



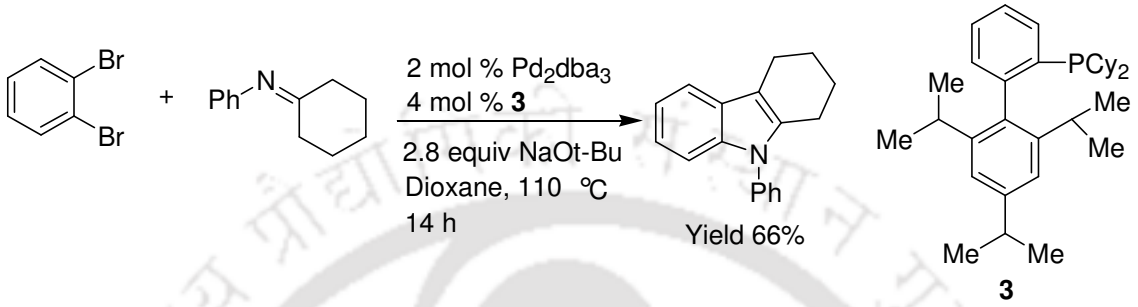
Scheme 6

Palladium-catalyzed sequential indole synthesis by using sterically hindered amines and bulky *N*-heterocyclic carbene **2** was reported by Ackermann and co-workers (Scheme 7).[7e] The reaction sequence consisting of an intermolecular *N*-arylation and an intramolecular hydroamination allowed for a regioselective *N*-annulation which then provides the desired indole derivatives.



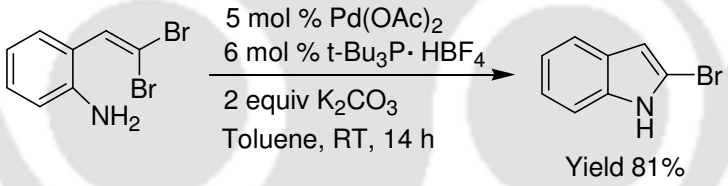
Scheme 7

Barluenga and co-workers have described palladium-catalyzed cascade process for synthesis of indoles from imines and *o*-dihaloarenes or *o*-chlorosulfonates (Scheme 8).[7f] The reaction involves two palladium catalyzed processes, an imine *C*-arylation and an intramolecular amination, both promoted by the same Pd catalyst.



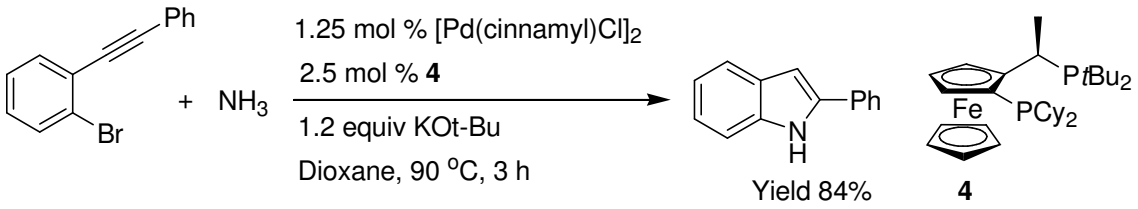
Scheme 8

Newman and Lautens have used palladium-catalyzed *C-N* bond formation protocol for construction of indole skeleton from *gem*-dibromoolefins.[7g] The reaction is effective to synthesize 2-bromoindole derivatives in good yields at ambient temperature (Scheme 9).



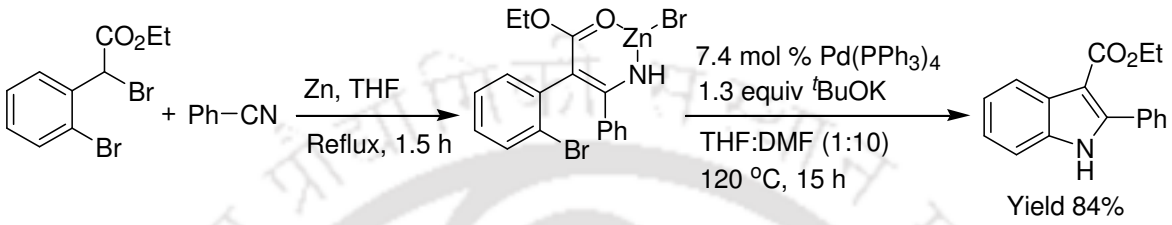
Scheme 9

The synthesis of indoles via the palladium-catalyzed cross-coupling of ammonia has been reported by Stradiotto and co-workers (Scheme 10).[7h] The other amines such methylamine or hydrazine are also cross-coupled to get the corresponding indoles.



Scheme 10

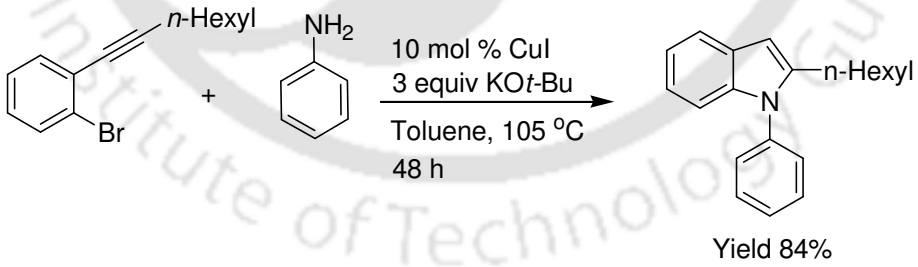
Lee and co-workers have reported a one-pot tandem protocol for the construction of indole moieties by the reaction of organozinc reagent (Reformatsky reagent) with nitriles i.e. Blaise reaction followed by palladium-catalyzed *C-N* cross-coupling reaction (Scheme 11).[7i] The aliphatic and aromatic nitriles readily undergo the reaction to give the desired indoles in good yields.



Scheme 11

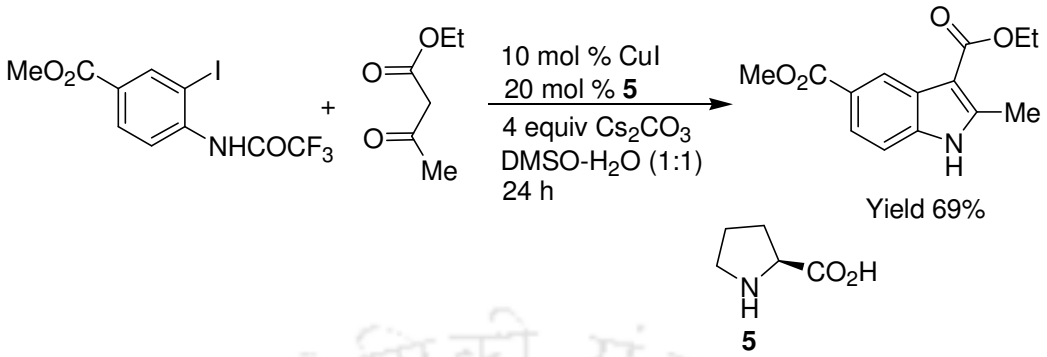
3.1.2 Copper catalysts

Copper catalysts with various ligands have been successfully employed for the synthesis of indole moieties in recent years. The synthesis of the indole skeleton starting from *o*-alkynylhaloarenes was reported by Ackermann by using copper-catalyzed amination and a subsequent cyclization reaction (Scheme 12).[8a] The reaction is efficient and works well in the presence of CuI and KO*t*-Bu in toluene.



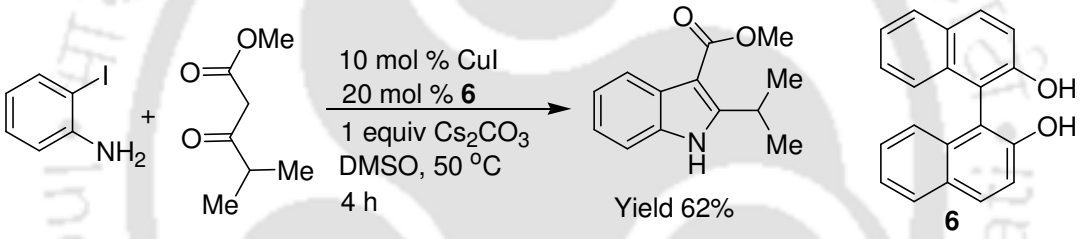
Scheme 12

Chen and co-workers have reported the CuI and L-proline **5** catalyzed cross-coupling of 2-halotrifluoroacetanilides with *β*-keto esters and amides followed by *in situ* acidic hydrolysis to prepare the 2,3-disubstituted indoles (Scheme 13).[8b]



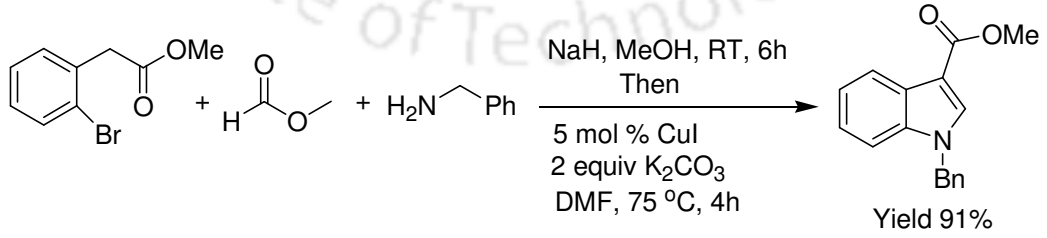
Scheme 13

Tanimori and co-workers reported one-step synthesis of 2,3-disubstituted indoles from readily available 2-iodoaniline and *β*-keto esters by using CuI and BINOL **6** system in the presence of base at 50 °C (Scheme 14).[8c]



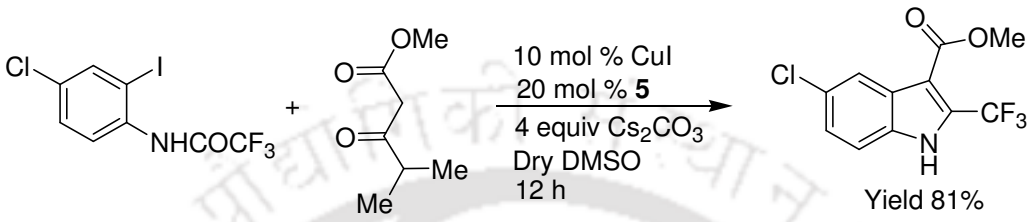
Scheme 14

The synthesis of *N*-substituted indole-3-carboxylic acid derivatives was reported by Karchava and co-workers *via* copper(I)-catalyzed intramolecular *C-N* bond formation (Scheme 15).[8d] The reaction conditions involves the use of CuI along with K_3PO_4 in DMF at 75 ˚C.



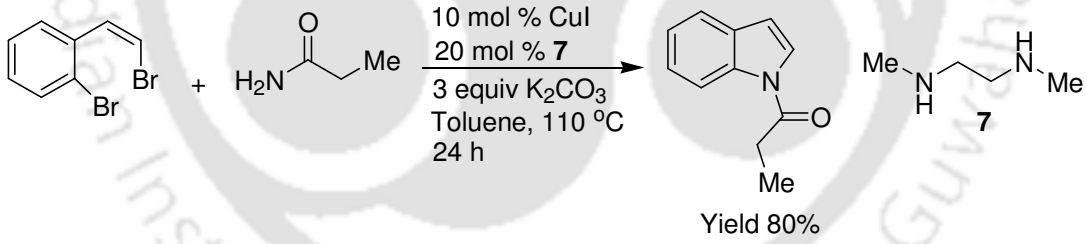
Scheme 15

Ma and co-workers reported CuI/L-proline ligand **5** catalyzed cross-coupling of 2-halotrifluoroacetanilides with *β*-keto esters in DMSO in the presence of Cs_2CO_3 at 40-80 °C (Scheme 16).[8e] A variety of functional groups remain unaffected under these conditions.



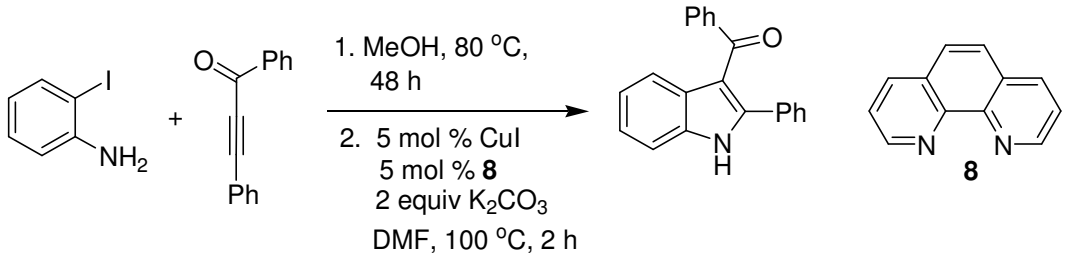
Scheme 16

A tandem *C-N* bond formation protocol on 2-(2-haloalkenyl)-aryl halide substrates to get a series of *N*-functionalised indoles have been developed by Willis and co-workers (Scheme 17).[8f] The conditions are very effective for the coupling of anilines, amides and carbamates with 2-(2-haloalkenyl)aryl halides to provide the corresponding indole moieties in the presence of CuI and *N,N'*-dimethylethylenediamine (DMEDA) **7**.



Scheme 17

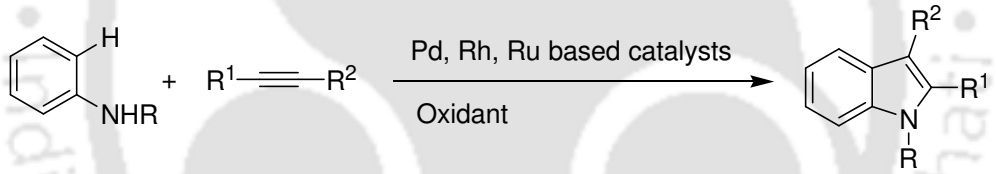
Bernini and co-workers have reported the synthesis of indoles from 2-haloanilines and *α,β*-ynones by sequential addition followed by copper-catalyzed cyclization process in the presence of CuI and 1.10-phenanthroline **8** (Scheme 18).[8g]



Scheme 18

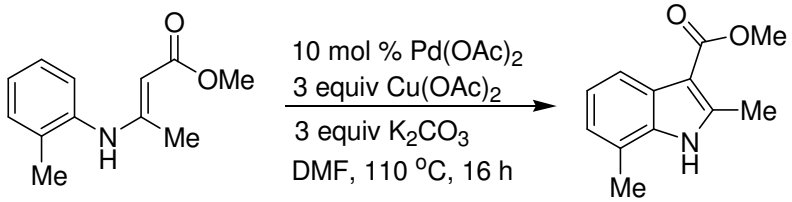
3.2 *C-H* Functionalization Methods

In recent years, *C-H* functionalization followed by *C-C/C-N* bond formation methods has been used for the synthesis of indole moieties. The most common approach is oxidative aniline–alkyne annulation approach to indoles by using palladium,[9a] rhodium[9b-d] and ruthenium[9e] based catalytic systems (Scheme 19).



Scheme 19

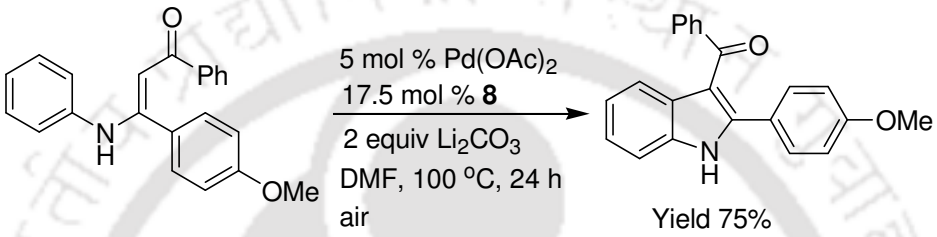
Glorius and co-workers have reported a palladium-catalyzed *C-H* activation and *C-C* bond formation methods of *N*-aryl enamines derived from anilines and *β*-dicarbonyl compounds to afford the corresponding substituted indoles (Scheme 20).[9f-g] This transformation of anilines into indoles can also be carried out in a one-pot sequence and a variety of anilines and *β*-dicarbonyl undergo oxidative cyclization to give the indole derivatives.



Yield 82%

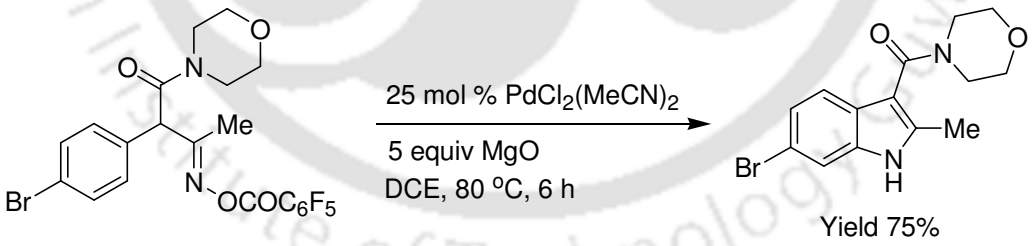
Scheme 20

A copper-catalyzed approach of Glorius method (Scheme 20) to the construction of multisubstituted indole skeletons from *N*-aryl enaminones has been developed by Cacchi and co-workers (Scheme 21).[9h] This method tolerates a variety of useful functional groups including the whole range of halogen substituents.



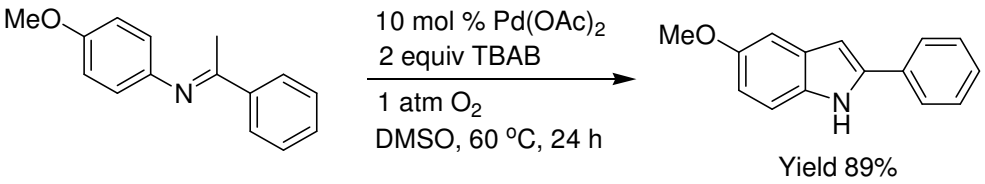
Scheme 21

Chiba and co-workers have developed a concise approach to substituted indoles using readily available and rather stable *O*-acyloximes via Pd(II)-catalyzed aromatic *C-H* amination (Scheme 22).[9i] The reaction works well in the presence of $PdCl_2(MeCN)_2$ catalyst and MgO base in 1,2-dichloroethane (DCE) solvent at 80 ˚C.



Scheme 22

A palladium-catalyzed cyclization of *N*-aryl imines via the oxidative linkage of two *C-H* bonds to get indoles derivatives under mild conditions using molecular oxygen as the sole oxidant was discovered by Yoshikai and co-workers (Scheme 23).[9j] The method is operationally simple and a variety of anilines and ketones undergo the reaction and exhibits very good functional group tolerance.



Scheme 23

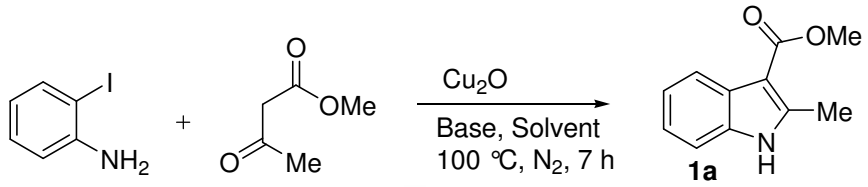
3.3 Present Study

The use of copper oxide as an active catalyst for the cross-coupling reactions has been demonstrated in recent years.[10,11] In this chapter, we report the synthesis of polysubstituted indoles by Cu_2O-catalyzed domino reaction of 2-haloanilines with a series of 1,3-dicarbonyl compounds, such as 1,3-diketone, *β*-keto ester and *β*-keto amide, in a 3:1 mixture of DMSO–water at moderate temperature. The procedure is simple, general, ligand-free and atom-economical for the synthesis of polysubstituted indoles.

First, the optimization of the reaction conditions was carried out with 2-iodoaniline and methyl acetoacetate as the model substrates (Table 1). The reaction occurred smoothly to afford the desired 2,3-disubstituted indole **1a** in 81% yield when the substrates were stirred with 10 mol % of Cu_2O and one equivalent of Cs_2CO_3 for 7 h at 100 °C in a 3:1 mixture of DMSO and water under a nitrogen atmosphere. Using DMSO, DMF, toluene, 1,4-dioxane and 2-propanol as the solvent afforded **1a** in 25–61% yields. Lowering the DMSO to water ratio led to **1a** in 51% yield. In the screened set of bases (K_2CO_3, KOH, K_3PO_4 and Cs_2CO_3), Cs_2CO_3 was found to be superior to others affording the best result. Replacing Cs_2CO_3 with K_2CO_3, KOH and K_3PO_4 as the base provided **1a** in 18–42% yields. Lowering the reaction temperature (80 °C) or the catalyst loading to 5 mol % led to production of **1a** in 48% or 54% yield, respectively. A control experiment confirmed that, without the copper reagent, no indole formation occurred.

Next, the scope of the procedure was studied for other substrates (Table 2). The reactions of 2-iodoanilines having 4-chloro, 4-nitro, 4-methyl, 4,5-dimethyl and 4,6-

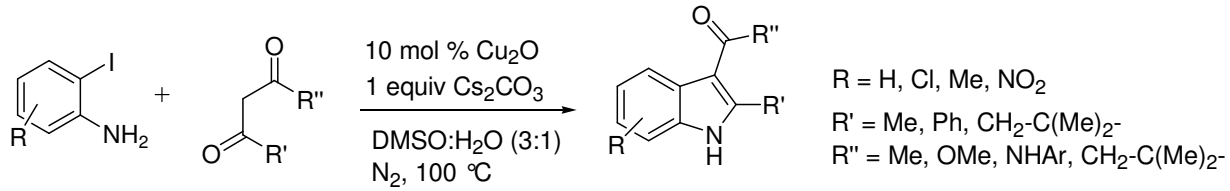
Table 1 Optimization of Reaction Conditions[a]

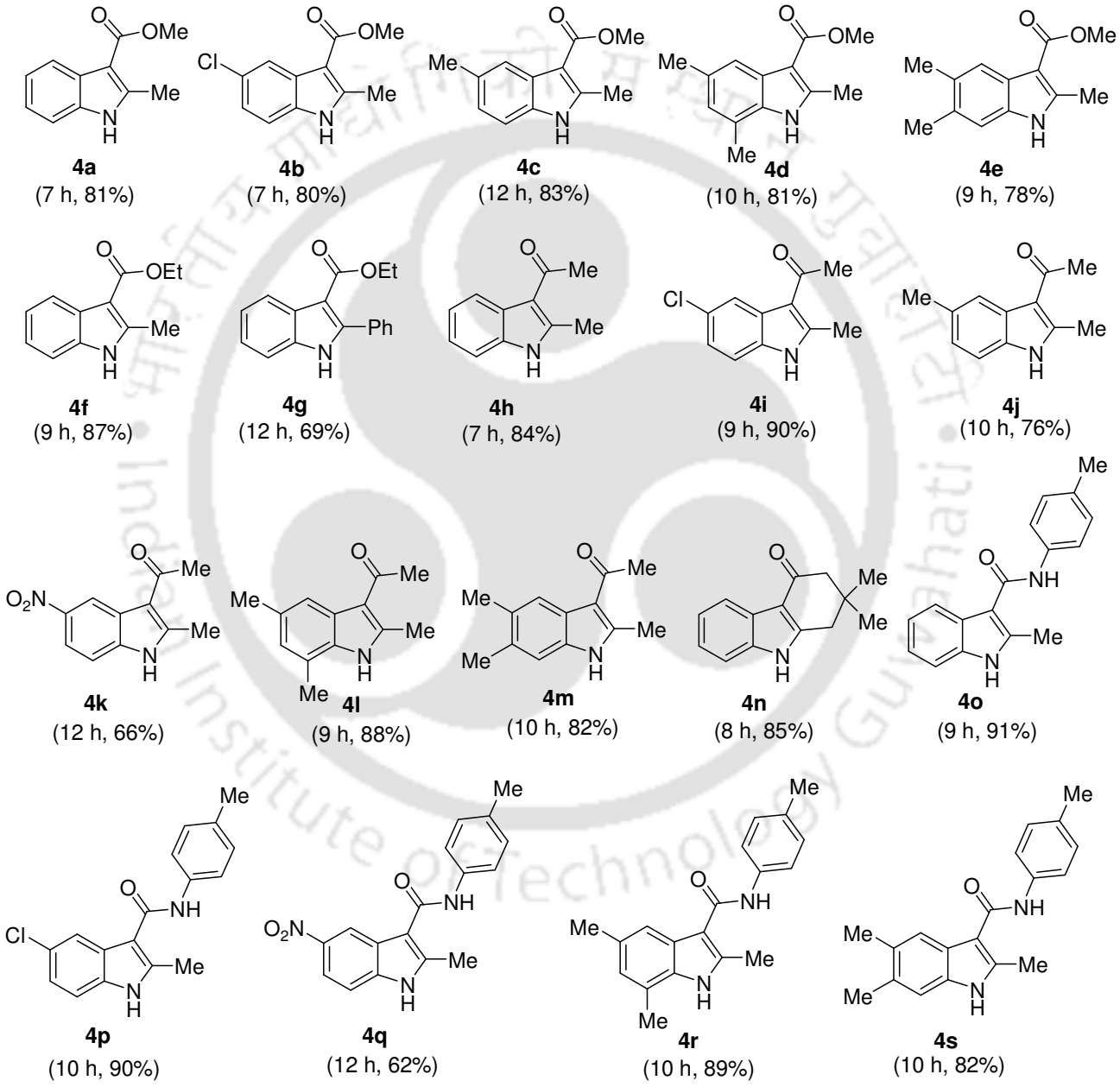


Entry	Solvent	Base	Yield (%)[b]
1	DMSO	Cs_2CO_3	60
2	DMF	Cs_2CO_3	45
3	Toluene	Cs_2CO_3	20
4	1,4-Dioxane	Cs_2CO_3	32
5	^{i}PrOH	Cs_2CO_3	25
6	DMSO-^{i}PrOH (1:1)	Cs_2CO_3	23
7	DMSO-H_2O (1:1)	Cs_2CO_3	51
8	DMSO-H_2O (3:1)	Cs_2CO_3	81
9	DMSO-H_2O (3:1)	K_2CO_3	42
10	DMSO-H_2O (3:1)	KOH	33
11	DMSO-H_2O (3:1)	K_3PO_4	18
12	DMSO-H_2O (3:1)	Cs_2CO_3	48[c]
13	DMSO-H_2O (3:1)	Cs_2CO_3	54[d]
14	DMSO-H_2O (3:1)	Cs_2CO_3	n.d.[e]

[a]Cu_2O (10 mol %), 2-iodoaniline (1 mmol), base (1 mmol) and methyl acetoacetate (1.2 mmol) were stirred at 100 °C for 7 h in solvent. [b]Isolated yield. [c]Temperature = 80 °C. [d]5 mol % Cu_2O used. [e]Cu_2O was not used.

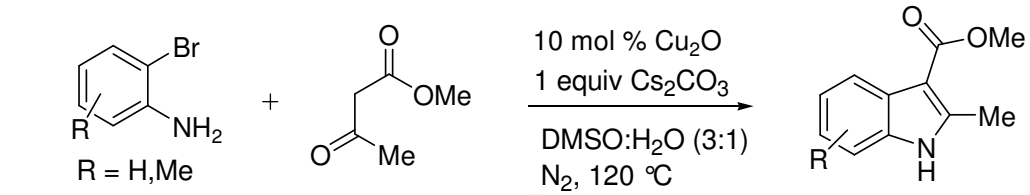
Table 2 Reaction of Amides with Substituted Aryl Iodides[a,b]

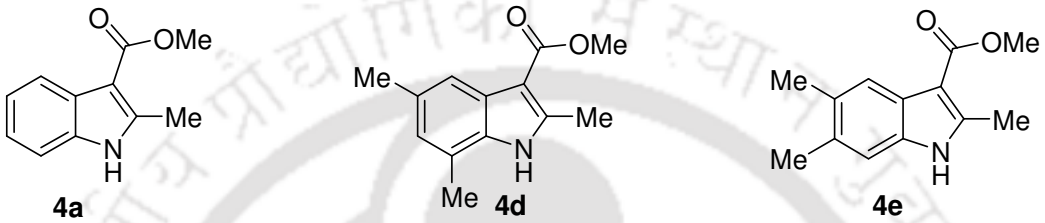




[a]Cu_2O (10 mol %), 2-iodoaniline (1 mmol), Cs_2CO_3 (1 mmol) and 1,3-dicarbonyl compound (1.2 mmol) were stirred at 100 °C in a 3:1 DMSO:H_2O (1 mL) under nitrogen atmosphere. [b]Isolated yield.

Table 3 Reactions 2-Bromoanilines and Methyl Acetoacetate[a,b]





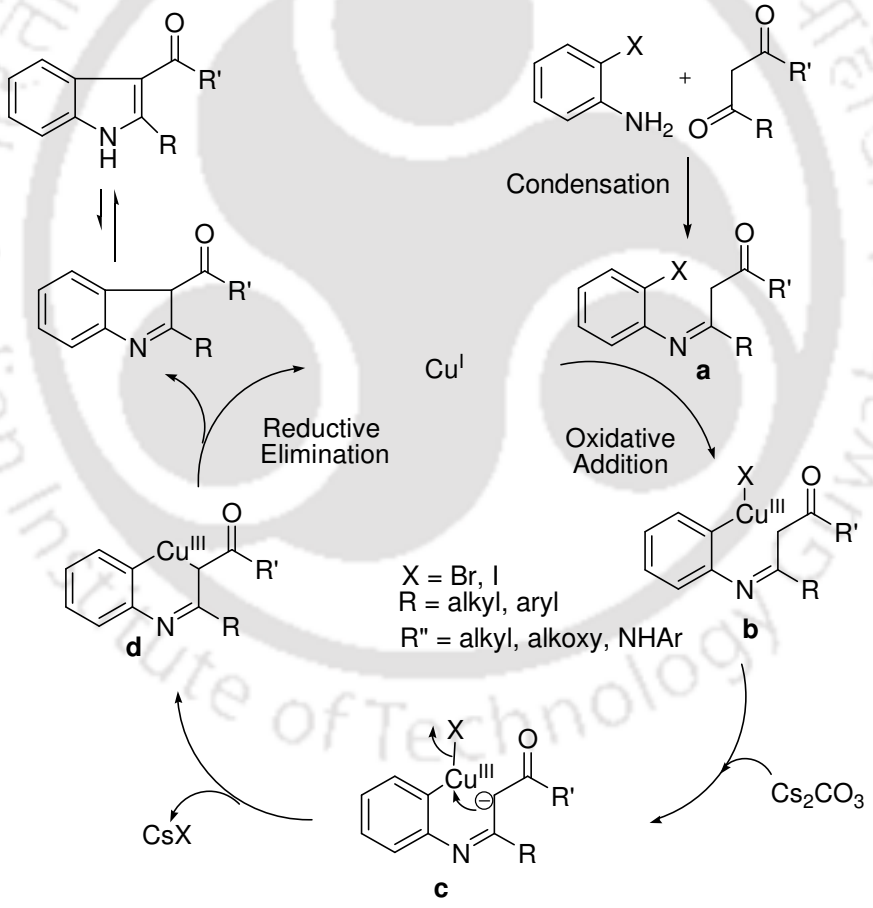
[a]Cu_2O (10 mol %), 2-bromoaniline (1 mmol), Cs_2CO_3 (1 mmol), and methyl acetoacetate (1.2 mmol) were stirred at 120 °C in a 3:1 DMSO:H_2O (1 mL) under nitrogen atmosphere. [b]Isolated yield.

dimethyl substituents were investigated with 1,3-dicarbonyl compounds, pentane-2,5-dione, 5,5-dimethylcyclohexane-1,3-dione, ethyl acetoacetate, methyl acetoacetate and 3-oxo-*N*-*p*-tolylbutanamide. All the substrates readily participated in the reaction to give the corresponding polysubstituted indoles **1b–s** in 7–12 h in 62–91% yields. The reactions were selective and no by-product was obtained. These results clearly suggest that the protocol is simple and general for the regiospecific synthesis of polysubstituted indoles in high yield.

Finally, the reactions of 2-bromoanilines with methyl acetoacetate were studied (Table 3). These reactions required slightly higher temperature to afford the products in 27–41% yields. Thus, 2-bromoaniline underwent reaction at 120 °C in 10 h to give **1a** in 27% yield. Likewise, 2-bromoaniline having 4,5-dimethyl and 4,6-dimethyl substituents provided the respective substituted indoles **1d** and **1e** in 12 h with 41% and 39% yield, respectively.

The proposed catalytic cycle is shown in Scheme 24. The reaction of iodobenzene with methyl acetoacetate was investigated using 10 mol % of Cu_2O and no intermolecular C–C cross-coupling was observed. On the other hand, aniline readily underwent condensation

with methyl acetoacetate to give the imine derivative in quantitative yield. These results suggest that the present protocol involves condensation followed by intramolecular C–C cross-coupling to afford the indoles. Thus, the condensation of 2-haloaniline with carbonyl compound can give imine derivative **a** that might undergo oxidative addition with Cu(I) to give the intermediate **b**. The latter with base could generate intermediate **c** which may transform into **d** by nucleophilic substitution. The intermediate **d** could complete the catalytic cycle by reductive elimination to generate the indole. During the oxidative addition, the C-X cleaves which is the possible rate determining step and as C-Br bond is stronger (bond energy 285 kJ/mole) than C-I bond (bond energy 213 kJ/mole), the reaction of 2-iodoanilines are faster than the 2-bromoamilines.



Scheme 24

In conclusion, the synthesis of polysubstituted indoles has been reported using the cheap, readily available, commercial Cu_2O as catalyst under ligand-free conditions. The

protocol is simple, general and atom economical for the regiospecific synthesis of polysubstituted indoles in high yield.

Experimental Section

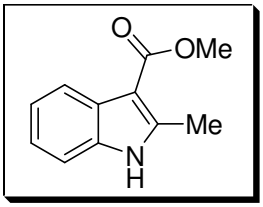
General Information

2-Haloanilines, Cu_2O powder <5 micron (97%), Cs_2CO_3, and K_3PO_4 were purchased from Aldrich and used without further purification. The column chromatography was performed with Rankem silica gel (60-120 mesh). NMR spectra (400 MHz for ^1H and 100 MHz for ^{13}C) were recorded using DRX-400 Varian spectrometer using $CDCl_3$ and DMSO-d_6 as solvent and Me_4Si as internal standard. Chemical shifts (δ) are reported in ppm and spin-spin coupling constants (J) are given in Hz. Melting points were determined using Buchi B-540 melting point apparatus and are uncorrected. FT-IR spectra were recorded using Perkin Elmer IR spectroscopy. Elemental analyses were recorded using Perkin Elmer CHNS analyzer.

General Procedure for Synthesis of Indoles

An oven-dried 10 mL round bottom flask was charged with 2-haloaniline (1 mmol), 1,3-dicarbonyl compoumd (1.2 mmol), Cu_2O (10 mol %), Cs_2CO_3 (1 mmol), DMSO:H_2O (3:1, 1 mL) and the mixture was stirred at 100 °C under nitrogen atmosphere. The progress of the reaction was monitored by TLC. After the completion of the reaction, the reaction mixture was cooled to room temperature and diluted with ethyl acetate (15 mL). The resulting solution was washed with brine (3 mL) and water (2 x 3 mL). Drying (Na_2SO_4) and evaporation of the solvent gave a residue that was purified by silica gel column chromatography using (10-20%) ethyl acetate in hexane as eluent.

Characterization Data of Products



Methyl 2-methyl-1*H*-indole-3-carboxylate[8c] (**4a**): 2-Iodoaniline (219 mg, 1 mmol), methyl acetoacetate (139 mg, 1.2 mmol), Cu_2O (14.3 mg, 10 mol %) and Cs_2CO_3 (326 mg, 1.0 mmol) were subjected to the reaction conditions described in the general procedure to afford the title compound as light yellow solid in 81% (153 mg) yield.

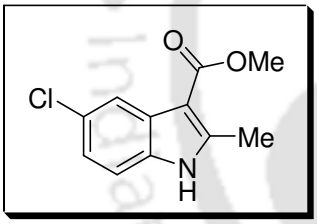
Mp: 165-166 °C (lit.[12a] 164-166 ºC).

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.44 (br s, 1H), 8.08 (d, *J* = 8.4 Hz, 1H), 7.30-7.16 (m, 3H), 3.92 (s, 3H), 2.73 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$:DMSO-d_6 (3:1)): δ 166.1, 144.5, 134.6, 126.8, 121.3, 120.7, 120.4, 110.6, 102.9, 50.1, 13.6.

FT-IR (KBr): 3291, 3269, 2946, 2923, 2851, 1666, 1547, 1489, 1456, 1440, 1332, 1270, 1199, 1116, 1091, 1015 cm^{-1}.

Anal. Calcd. for $C_{11}H_{11}NO_2$: C, 69.83; H, 5.86; N, 7.40. Found: C, 69.77; H, 5.84; N, 7.44.



Methyl 5-chloro-2-methyl-1*H*-indole-3-carboxylate (**4b**): 4-Chloro-2-iodoaniline (254 mg, 1 mmol), methyl acetoacetate (139 mg, 1.2 mmol), Cu_2O (14.3 mg, 10 mol %) and Cs_2CO_3 (326 mg, 1.0 mmol) were subjected to the reaction conditions described in the general procedure to afford the title compound as light brown solid in 80% (179 mg) yield.

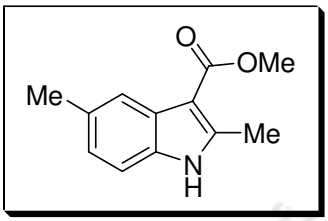
Mp: 173-174 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.38 (br s, 1H), 8.06 (s, 1H), 7.23 (d, *J* = 8.0 Hz, 1H), 7.16 (dd, *J* = 8.4, 2.0 Hz, 1H), 3.94 (s, 3H) 2.74 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$:DMSO-d_6 (3:1)): δ 166.2, 146.1, 133.3, 128.3, 126.8, 121.9, 120.4, 111.9, 103.4, 50.7, 14.1.

FT-IR (KBr): 3290, 2947, 2857, 1662, 1462, 1437, 1294, 1196, 1103 cm^{-1}.

Anal. Calcd. for $C_{11}H_{10}ClNO_2$: C, 59.07; H, 4.51; N, 6.26. Found: C, 59.00; H, 4.48; N, 6.22.



Methyl 2,5-dimethyl-1*H*-indole-3-carboxylate (**4c**): 2-Iodo-4-methylaniline (233 mg, 1 mmol), methyl acetoacetate (139 mg, 1.2 mmol), Cu_2O (14.3 mg, 10 mol %) and Cs_2CO_3 (326 mg, 1.0 mmol) were subjected to the reaction conditions described in the general procedure to afford the title compound as white solid in 83% (169 mg) yield.

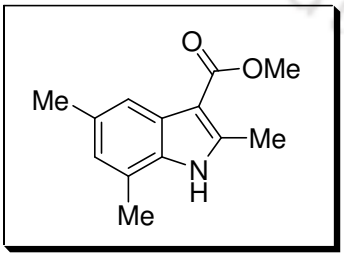
Mp: 168-169 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.33 (br s, 1H), 7.86 (s, 1H), 7.17 (d, *J* = 8.0 Hz, 1H), 7.00 (d, *J* = 9.2 Hz, 1H), 3.91 (s, 3H), 2.70 (s, 3H), 2.45 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 167.1, 144.6, 133.0, 131.2, 127.5, 123.9, 120.9, 110.5, 103.7, 50.9, 21.8, 14.3.

FT-IR (KBr): 3305, 3005, 2943, 2857, 1673, 1541, 1473, 1445, 1421, 1334, 1299, 1276, 1210, 1191, 1157, 1095 $cm^{-1.}$

Anal. Calcd. for $C_{12}H_{13}NO_2$: C, 70.92; H, 6.45; N, 6.89. Found: C, 70.86; H, 6.43; N, 6.93.



Methyl 2,5,7-trimethyl-1*H*-indole-3-carboxylate (**4d**): 2-Iodo-4,6-dimethylaniline (247 mg, 1 mmol), methyl acetoacetate (139 mg, 1.2 mmol), Cu_2O (14.3 mg, 10 mol %) and

Cs_2CO_3 (326 mg, 1.0 mmol) were subjected to the reaction conditions described in the general procedure to afford the title compound as white solid in 81% (176 mg) yield.

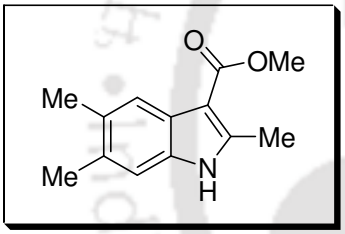
Mp: 196-198 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.18 (br s, 1H), 7.70 (s, 1H), 6.82 (s, 1H), 3.91 (s, 3H), 2.72 (s, 3H), 2.42 (s, 6H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 166.9, 144.5, 132.6, 130.8, 127.1, 124.3, 119.8, 118.2, 103.5, 50.6, 21.5, 16.6, 14.1.

FT-IR (KBr): 3306, 3000, 2953, 2914, 2851, 1649, 1477, 1456, 1380, 1365, 1309, 1293, 1238, 1226, 1193, 1147, 1109, 1083 cm^{-1}.

Anal. Calcd. for $C_{13}H_{15}NO_2$: C, 71.87; H, 6.96; N, 6.45. Found: C, 71.81; H, 6.98; N, 6.41.



Methyl 2,5,6-trimethyl-1*H*-indole-3-carboxylate (**4e**): 2-Iodo-4,5-dimethylaniline (247 mg, 1 mmol), methyl acetoacetate (139 mg, 1.2 mmol), Cu_2O (14.3 mg, 10 mol %) and Cs_2CO_3 (326 mg, 1.0 mmol) were subjected to the reaction conditions described in the general procedure to afford the title compound as white solid in 78% (170 mg) yield.

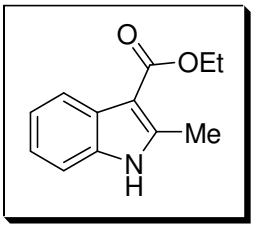
Mp: 207-208 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.15 (br s, 1H), 7.81 (s, 1H), 7.04 (s, 1H), 3.90 (s, 3H), 2.69 (s, 3H), 2.35 (s, 3H), 2.32 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$:DMSO-d_6 (3:1)): δ 166.8, 143.8, 133.7, 130.7, 129.8, 125.5, 121.0, 111.3, 103.1, 50.5, 20.2, 20.1, 14.1.

FT-IR (KBr): 3294, 2956, 2917, 2851, 1659, 1468, 1418, 1208, 1118, 1089 cm^{-1}.

Anal. Calcd. for $C_{13}H_{15}NO_2$: C, 71.87; H, 6.96; N, 6.45. Found: C, 71.82; H, 6.94; N, 6.42.



Ethyl 2-methyl-1*H*-indole-3-carboxylate[12b] (**4f**): 2-Iodoaniline (219 mg, 1 mmol), ethyl acetoacetate (156 mg, 1.2 mmol), Cu_2O (14.3 mg, 10 mol %) and Cs_2CO_3 (326 mg, 1.0 mmol) were subjected to the reaction conditions described in the general procedure to afford the title compound as white solid in 87% (177 mg) yield.

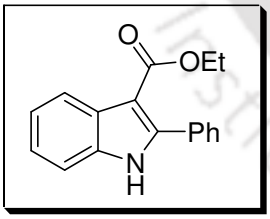
Mp: 134-136 °C (lit.[12b] 135-136 ºC).

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.38 (br s, 1H), 8.10 (d, *J* = 7.6 Hz, 1H), 7.31-7.17 (m, 3H), 4.40 (q, *J* = 6.8 Hz, 2H), 2.75 (s, 3H), 1.45 (t, *J* = 6.8 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 166.6, 144.5, 134.8, 127.4, 122.4, 121.8, 121.3, 110.9, 104.5, 59.8, 14.7, 14.3.

FT-IR (KBr): 3305, 2976, 2926, 1658, 1548, 1458, 1334, 1274, 1199, 1122, 1093, 1016 cm^{-1}.

Anal. Calcd. for $C_{12}H_{13}NO_2$: C, 70.92; H, 6.45; N, 6.89. Found: C, 70.87; H, 6.42; N, 6.93.



Ethyl 2-phenyl-1*H*-indole-3-carboxylate[12b] (**4g**): 2-Iodoaniline (219 mg, 1 mmol), ethyl 3-oxo-3-phenylpropanoate (231 mg, 1.2 mmol), Cu_2O (14.3 mg, 10 mol %) and Cs_2CO_3 (326 mg, 1.0 mmol) were subjected to the reaction conditions described in the general procedure to afford the title compound as white solid in 69% (183 mg) yield.

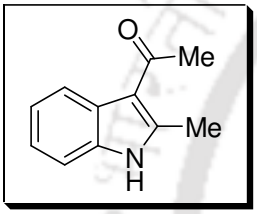
Mp: 157-158 °C (lit.[12b] 156-158 ºC).

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.85 (br s, 1H), 8.11 (d, *J* = 7.2 Hz, 1H), 7.50-7.47 (m, 2H), 7.26-7.25 (m, 3H), 7.21-7.11 (m, 3H), 4.14 (q, *J* = 6.8 Hz, 2H), 1.18 (t, *J* = 7.2 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 165.8, 144.9, 135.4, 132.2, 129.8, 129.2, 128.2, 127.8, 123.2, 122.2, 122.1, 111.4, 104.6, 59.9, 14.4.

FT-IR (KBr): 3307, 3273, 3059, 2987, 2939, 2902, 1682, 1666, 1550, 1487, 1475, 1446, 1427, 1389, 1333, 1281, 1213, 1198, 1128, 1111, 1050, 1027 cm^{-1}.

Anal. Calcd. for $C_{17}H_{15}NO_2$: C, 76.96; H, 5.70; N, 5.28. Found: C, 76.89; H, 5.68; N, 5.22.



1-(2-Methyl-1*H*-indol-3-yl)ethanone (**4h**): 2-Iodoaniline (219 mg, 1 mmol), acetylacetone (120 mg, 1.2 mmol), Cu_2O (14.3 mg, 10 mol %) and Cs_2CO_3 (326 mg, 1.0 mmol) were subjected to the reaction conditions described in the general procedure to afford the title compound as light yellow solid in 84% (146 mg) yield.

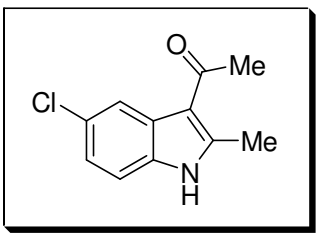
Mp: 201-202 °C (lit.[12c] 200-201 ºC).

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.49 (br s, 1H), 8.01 (d, *J* = 8.4 Hz, 1H), 7.32 (d, *J* = 7.6 Hz, 1H), 7.26-7.20 (m, 2H), 2.76 (s, 3H), 2.66 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$:DMSO-d_6 (3:1)): δ 193.9, 144.2, 134.7, 126.7, 123.7, 121.5, 121.2, 120.3, 110.9, 30.7, 14.9.

FT-IR (KBr): 3453, 3428, 2928, 1615, 1580, 1456, 1437, 1261, 1100, 1067, 1020 cm^{-1}.

Anal. Calcd. for $C_{11}H_{11}NO$: C, 76.28; H, 6.40; N, 8.09. Found: C, 76.21; H, 6.37; N, 8.05.



1-(5-Chloro-2-methyl-1*H*-indol-3-yl)ethanone (**4i**): 4-Chloro-2-iodoaniline (254 mg, 1 mmol), acetylacetone (120 mg, 1.2 mmol), Cu_2O (14.3 mg, 10 mol %) and Cs_2CO_3 (326 mg, 1.0 mmol) were subjected to the reaction conditions described in the general procedure to afford the title compound as light brown solid in 90% (187 mg) yield.

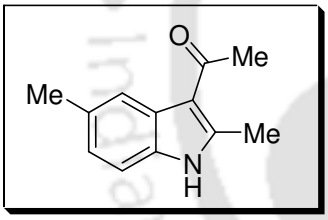
Mp: 264-265 °C.

^{1}H NMR (400 MHz, DMSO-d_6): δ 12.00 (br s, 1H), 8.04 (d, *J* = 2.0 Hz, 1H), 7.37 (d, *J* = 8.4 Hz, 1H), 7.15 (dd, *J* = 8.4, 2.0 Hz, 1H), 2.68 (s, 3H), 2.49 (s, 3H).

^{13}C NMR (100 MHz, DMSO-d_6): δ 192.9, 145.6, 133.2, 128.2, 126.0, 121.7, 119.9, 113.3, 112.6, 30.6, 15.0.

FT-IR (KBr): 3205, 3181, 2989, 1621, 1610, 1574, 1456, 1447, 1418, 1386, 1263, 1200, 1055, 1024 cm^{-1}.

Anal. Calcd. for $C_{11}H_{10}ClNO$: C, 63.62; H, 4.85; N, 6.75. Found: C, 63.58; H, 4.86; N, 6.71.



1-(2,5-Dimethyl-1*H*-indol-3-yl)ethanone (**4j**): 2-Iodo-4-methylaniline (233 mg, 1 mmol), acetylacetone (120 mg, 1.2 mmol), Cu_2O (14.3 mg, 10 mol %) and Cs_2CO_3 (326 mg, 1.0 mmol) were subjected to the reaction conditions described in the general procedure to afford the title compound as yellow solid in 76% (142 mg) yield.

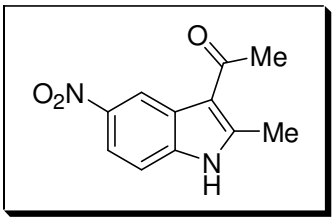
Mp: 236-238 °C.

^{1}H NMR (400 MHz, DMSO-d_6): δ 11.68 (br s, 1H), 7.79 (s, 1H), 7.21 (d, *J* = 8.0 Hz, 1H), 6.93 (d, *J* = 8.4 Hz, 1H), 2.63 (s, 3H), 2.47 (s, 3H), 2.37 (s, 3H).

^{13}C NMR (100 MHz, DMSO-d_6): δ 192.9, 144.1, 132.9, 129.9, 127.2, 123.1, 120.5, 117.8, 110.8, 30.9, 21.4, 15.0.

FT-IR (KBr): 3214, 3187, 3051, 2917, 2857, 1724, 1621, 1608, 1585, 1452, 1419, 1217, 1071, 1028 cm^{-1}.

Anal. Calcd. for $C_{12}H_{13}NO$: C, 76.98; H, 7.00; N, 7.48. Found: C, 76.95; H, 6.98; N, 7.53.



1-(2-Methyl-5-nitro-1*H*-indol-3-yl)ethanone (**4k**): 2-Iodo-4-nitroaniline (264 mg, 1 mmol), acetylacetone (120 mg, 1.2 mmol), Cu_2O (14.3 mg, 10 mol %) and Cs_2CO_3 (326 mg, 1.0 mmol) were subjected to the reaction conditions described in the general procedure to afford the title compound as brown solid in 66% (144 mg) yield.

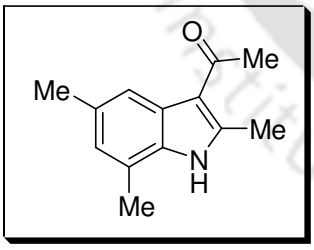
Mp: 281-283 °C.

^{1}H NMR (400 MHz, DMSO-d_6): δ 11.55 (s, 1H), 8.48 (s, 1H), 7.52 (d, *J* = 8.8 Hz, 1H), 6.92 (dd, *J* = 8.8, 2.4 Hz, 1H), 2.26 (s, 3H), 2.10 (s, 3H).

^{13}C NMR (100 MHz, DMSO-d_6): δ 193.9, 148.2, 142.6, 138.3, 126.7, 117.8, 117.4, 115.1, 111.9, 30.8, 15.3.

FT-IR (KBr): 3200, 3075, 2958, 2925, 2855, 1732, 1615, 1582, 1541, 1514, 1468, 1419, 1333, 1264, 1202, 1186, 1122, 1077, 1021 cm^{-1}.

Anal. Calcd. for $C_{11}H_{10}N_2O_3$: C, 60.55; H, 4.62; N, 12.84. Found: C, 60.51; H, 4.59; N, 12.89.



1-(2,5,7-Trimethyl-1*H*-indol-3-yl)ethanone (**4l**): 2-Iodo-4,6-dimethylaniline (247 mg, 1 mmol), acetylacetone (120 mg, 1.2 mmol), Cu_2O (14.3 mg, 10 mol %) and Cs_2CO_3 (326 mg, 1.0 mmol) were subjected to the reaction conditions described in the general procedure to afford the title compound as yellow solid in 88% (177 mg) yield.

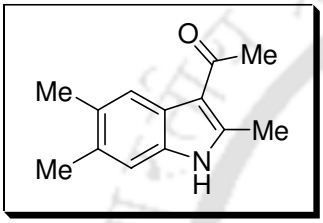
Mp: 225-226 °C.

^{1}H NMR (400 MHz, DMSO-d_6): δ 11.53 (s, 1H), 7.64 (s, 1H), 6.76 (s, 1H), 2.67 (s, 3H), 2.48 (s, 3H), 2.42 (s, 3H), 2.35 (s, 3H).

^{13}C NMR (100 MHz, DMSO-d_6): δ 193.0, 143.9, 132.5, 129.9, 126.9, 123.9, 119.9, 118.1, 113.6, 30.9, 21.4, 16.6, 14.9.

FT-IR (KBr): 3200, 3131, 3053, 2956, 2918, 2851, 1732, 1606, 1593, 1453, 1421, 1295, 1068, 1020 cm^{-1}.

Anal. Calcd. for $C_{13}H_{15}NO$: C, 77.58; H, 7.51; N, 6.96. Found: C, 77.53; H, 7.53; N, 6.93.



1-(2,5,6-Trimethyl-1*H*-indol-3-yl)ethanone (**4m**): 2-Iodo-4,5-dimethylaniline (247 mg, 1 mmol), acetylacetone (120 mg, 1.2 mmol), Cu_2O (14.3 mg, 10 mol %) and Cs_2CO_3 (326 mg, 1.0 mmol) were subjected to the reaction conditions described in the general procedure to afford the title compound as yellow solid in 82% (165 mg) yield.

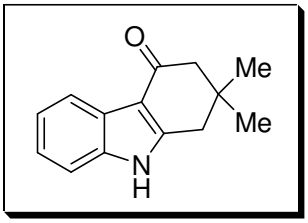
Mp: 257-258 °C.

^{1}H NMR (400 MHz, DMSO-d_6): δ 11.58 (br s, 1H), 7.77 (s, 1H), 7.12 (s, 1H), 2.63 (s, 3H), 2.48 (s, 3H), 2.29 (s, 3H), 2.28 (s, 3H).

^{13}C NMR (100 MHz, DMSO-d_6): δ 192.8, 143.2, 133.6, 130.0, 129.2, 123.8, 120.9, 118.5, 111.4, 30.8, 20.0, 19.9, 14.9.

FT-IR (KBr): 3208, 3175, 3137, 3087, 2962, 2917, 2851, 1725, 1716, 1609, 1572, 1457, 1415, 1385, 1261, 1208, 1163, 1102, 1067, 1018 cm^{-1}.

Anal. Calcd. for $C_{13}H_{15}NO$: C, 77.58; H, 7.51; N, 6.96. Found: C, 77.52; H, 7.48; N, 6.91.



2,2-Dimethyl-2,3-dihydro-1*H*-carbazol-4(9H)-one[12d] (**4n**): 2-Iodoaniline (219 mg, 1 mmol), diimidone (168 mg, 1.2 mmol), Cu_2O (14.3 mg, 10 mol %) and Cs_2CO_3 (326 mg, 1.0 mmol) were subjected to the reaction conditions described in the general procedure to afford the title compound as white solid in 85% (181 mg) yield.

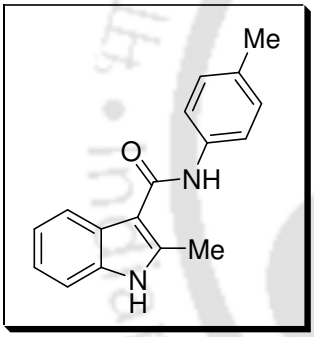
Mp: 194-195 °C (lit.[12d] 195-196 ºC).

^{1}H NMR (400 MHz, $CDCl_3$): δ 9.12 (br s, 1H), 8.22 (d, *J* = 8.0 Hz, 1H), 7.37 (d, *J* = 8.4 Hz, 1H), 7.27-7.21 (m, 2H), 2.84 (s, 2H), 2.47 (s, 2H), 1.15 (s, 6H).

^{13}C NMR (100 MHz, $CDCl_3$:DMSO-d_6 (3:1)): δ 193.3, 150.9, 136.3, 124.6, 122.4, 121.7, 120.7, 111.2, 52.2, 37.0, 35.4, 28.4.

FT-IR (KBr): 3217, 3186, 2959, 2926, 2868, 1624, 1612, 1471, 1456, 1100, 1059 cm^{-1}.

Anal. Calcd. for $C_{14}H_{15}NO$: C, 78.84; H, 7.09; N, 6.57. Found: C, 78.78; H, 7.07; N, 6.61.



2-Methyl-*N*-*p*-tolyl-1*H*-indole-3-carboxamide (**4o**): 2-Iodoaniline (219 mg, 1 mmol), 3-oxo-*N*-p-tolylbutyramide (229 mg, 1.2 mmol), Cu_2O (14.3 mg, 10 mol %) and Cs_2CO_3 (326 mg, 1.0 mmol) were subjected to the reaction conditions described in the general procedure to afford the title compound as light yellow solid in 91% (241 mg) yield.

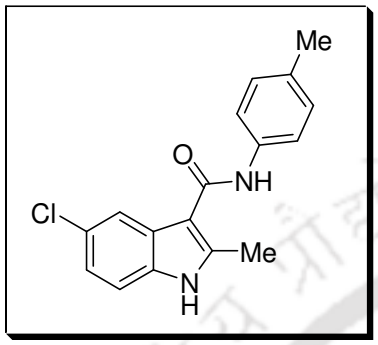
Mp: 205-206 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.51 (s, 1H), 7.78 (d, *J* = 7.6 Hz, 1H), 7.66 (s, 1H), 7.52 (d, *J* = 6.8 Hz, 2H), 7.35 (dd, *J* = 6.8, 2.0 Hz, 1H), 7.26-7.16 (m, 4H), 2.74 (s, 3H), 2.34 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$:DMSO-d_6 (3:1)): δ 164.4, 141.0, 136.1, 134.8, 132.5, 128.9, 125.5, 121.1, 120.3, 119.8, 118.3, 111.1, 107.5, 20.4, 13.1.

FT-IR (KBr): 3257, 3054, 2919, 2851, 1608, 1552, 1518, 1494, 1456, 1421, 1403, 1326, 1240, 1198, 1119, 1083, 1021 cm^{-1}.

Anal. Calcd. for $C_{17}H_{16}N_2O$: C, 77.25; H, 6.10; N, 10.60. Found: C, 77.18; H, 6.08; N, 10.65.



5-Chloro-2-Methyl-*N*-*p*-tolyl-1*H*-indole-3-carboxamide (**4p**): 4-Chloro-2-iodoaniline (254 mg, 1 mmol), 3-oxo-*N*-p-tolylbutyramide (229 mg, 1.2 mmol), Cu_2O (14.3 mg, 10 mol %) and Cs_2CO_3 (326 mg, 1.0 mmol) were subjected to the reaction conditions described in the general procedure to afford the title compound as grey yellow solid in 90% (269 mg) yield.

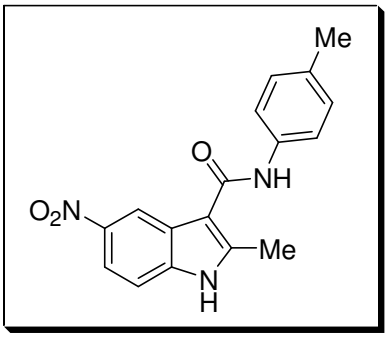
Mp: 232-234 °C.

^{1}H NMR (400 MHz, DMSO-d_6): δ 11.75 (s, 1H), 9.55 (s, 1H), 7.70 (s, 1H), 7.60 (d, *J* = 8.8 Hz, 1H), 7.37 (d, *J* = 8.8 Hz, 1H), 7.13 (m, 3H), 2.61 (s, 3H), 2.28 (s, 3H).

^{13}C NMR (100 MHz, DMSO-d_6): δ 163.6, 141.1, 137.2, 133.2, 131.9, 128.9, 127.6, 124.7, 121.1, 120.0, 118.8, 112.5, 108.6, 20.5, 13.2.

FT-IR (KBr): 3280, 3252, 3225, 3032, 2921, 2851, 1602, 1573, 1518, 1496, 1469, 1427, 1241, 1199, 1097, 1066, 1019 cm^{-1}.

Anal. Calcd. for $C_{17}H_{15}ClN_2O$: C, 68.34; H, 5.06; N, 9.38.Found: C, 68.42; H, 5.08; N, 9.33.



2-Methyl-5-nitro-*N*-*p*-tolyl-1*H*-indole-3-carboxamide (**4q**): 2-Iodo-4-nitroaniline (264 mg, 1 mmol), 3-oxo-*N*-p-tolylbutyramide (229 mg, 1.2 mmol), Cu_2O (14.3 mg, 10 mol %) and Cs_2CO_3 (326 mg, 1.0 mmol) were subjected to the reaction conditions described in the general procedure to afford the title compound as deep brown solid in 62% (192 mg) yield.

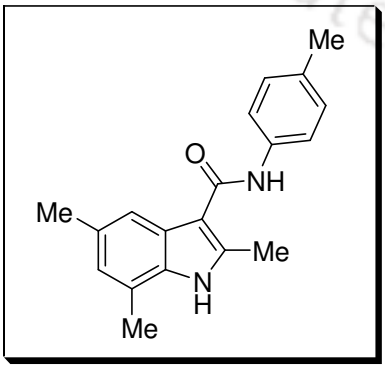
Mp: 232-233 °C.

^{1}H NMR (400 MHz, DMSO-d_6): δ 12.24 (s, 1H), 9.76 (s, 1H), 8.63 (s, 1H), 8.03 (d, *J* = 8.8 Hz, 1H), 7.60 (d, *J* = 6.8 Hz, 2H), 7.55 (d, *J* = 8.8 Hz, 1H), 7.15 (d, *J* = 7.2 Hz, 2H), 2.65 (s, 3H), 2.29 (s, 3H).

^{13}C NMR (100 MHz, DMSO-d_6): δ 163.6, 143.6, 142.0, 138.7, 137.5, 132.9, 129.7, 126.6, 120.8, 117.5, 116.9, 112.2, 111.5, 21.2, 13.9.

FT-IR (KBr): 3295, 2960, 2924, 2854, 1740, 1634, 1597, 1519, 1509, 1478, 1462, 1422, 1401, 1330, 1313, 1297, 1261, 1241, 1196, 1099, 1064, 1023 cm^{-1}.

Anal. Calcd. for $C_{17}H_{15}N_3O_3$: C, 66.01; H, 4.89; N, 13.58. Found: C, 65.94; H, 4.87; N, 13.63.



2,5,7-Trimethyl-*N*-*p*-tolyl-1*H*-indole-3-carboxamide (**4r**): 2-Iodo-4,6-dimethylaniline (247 mg, 1 mmol), 3-oxo-*N*-p-tolylbutyramide (229 mg, 1.2 mmol), Cu_2O (14.3 mg, 10 mol %) and Cs_2CO_3 (326 mg, 1.0 mmol) were subjected to the reaction conditions described in the general procedure to afford the title compound as light brown solid in 89% (260 mg) yield.

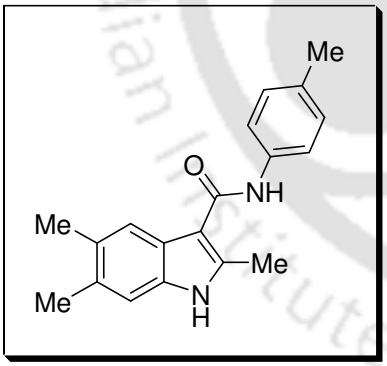
Mp: 217-218 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.15 (s, 1H), 7.63 (s, 1H), 7.50 (d, *J* = 7.6 Hz, 2H), 7.38 (s, 1H), 7.15 (d, *J* = 8.4 Hz, 2H), 6.85 (s, 1H), 2.74 (s, 3H), 2.45 (s, 3H), 2.44 (s, 3H), 2.33 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$:DMSO-d_6 (3:1)): δ 164.8, 141.8, 136.2, 133.0, 132.8, 130.5, 129.4, 125.5, 124.0, 120.6, 120.0, 115.7, 107.6, 21.6, 20.8, 16.8, 13.6.

FT-IR (KBr): 3422, 3199, 2919, 2856, 1637, 1607, 1593, 1516, 1456, 1402, 1310, 1245, 1233, 1160, 1152, 1105, 1018 cm^{-1}.

Anal. Calcd. for $C_{19}H_{20}N_2O$: C, 78.05; H, 6.89; N, 9.58. Found: C, 78.00; H, 6.86; N, 9.55.



2,5,6-Trimethyl-*N*-*p*-tolyl-1*H*-indole-3-carboxamide (**4s**): 2-Iodo-4,5-dimethylaniline (247 mg, 1 mmol), 3-oxo-*N*-p-tolylbutyramide (229 mg, 1.2 mmol), Cu_2O (14.3 mg, 10 mol %) and Cs_2CO_3 (326 mg, 1.0 mmol) were subjected to the reaction conditions described in the general procedure to afford the title compound as light brown solid in 82% (240 mg) yield.

Mp: 227-228 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.16 (s, 1H), 7.62 (s, 1H), 7.50 (d, *J* = 7.2 Hz, 3H), 7.15 (d, *J* = 8.0 Hz, 2H), 7.11 (s, 1H), 2.70 (s, 3H), 2.36 (s, 3H), 2.34 (s, 3H), 2.33 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$:DMSO-d_6 (3:1)): δ 164.5, 140.3, 136.2, 133.7, 132.3, 129.9, 128.9, 123.8, 119.7, 118.6, 111.5, 106.8, 20.5, 19.9, 19.8, 13.2.

FT-IR (KBr): 3403, 3269, 2917, 2857, 1633, 1621, 1593, 1542, 1515, 1494, 1448, 1402, 1309, 1262, 1238, 1196, 1173, 1115, 1023 cm^{-1}.

Anal. Calcd. for $C_{19}H_{20}N_2O$: C, 78.05; H, 6.89; N, 9.58. Found: C, 77.98; H, 6.85; N, 9.60.

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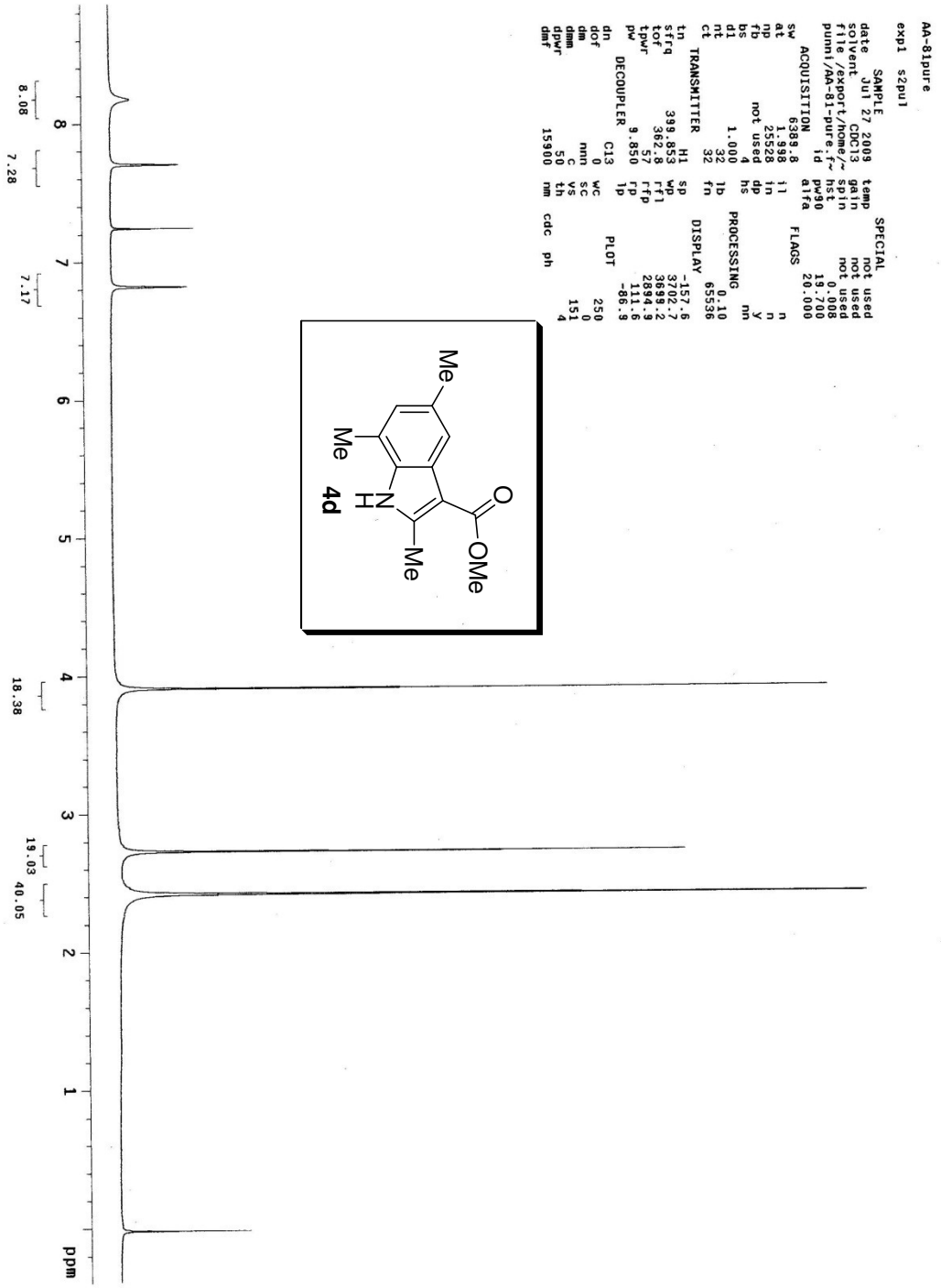
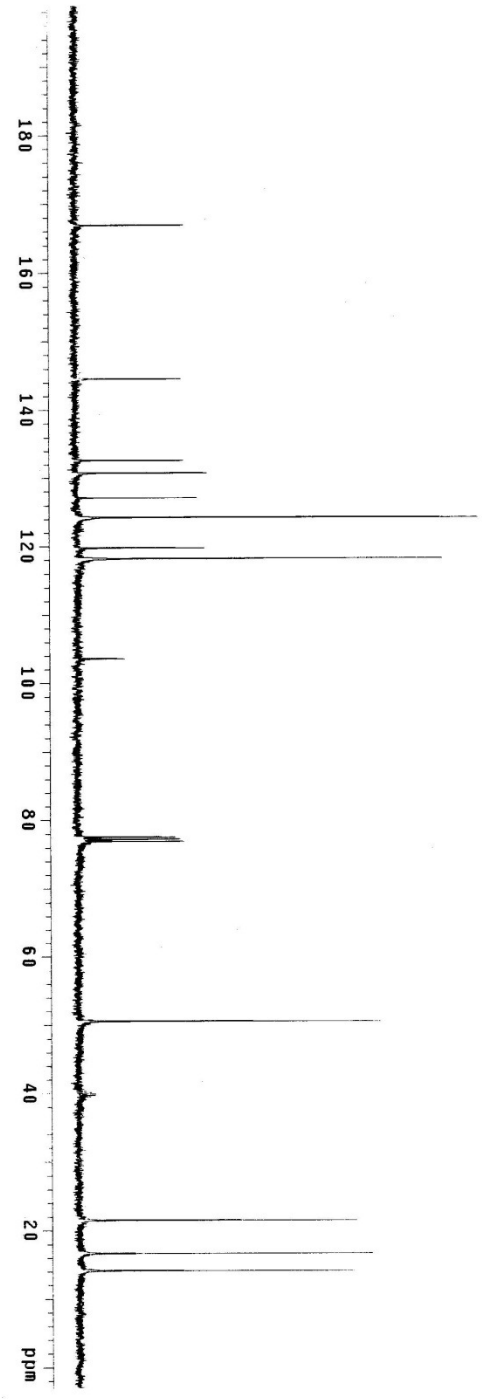
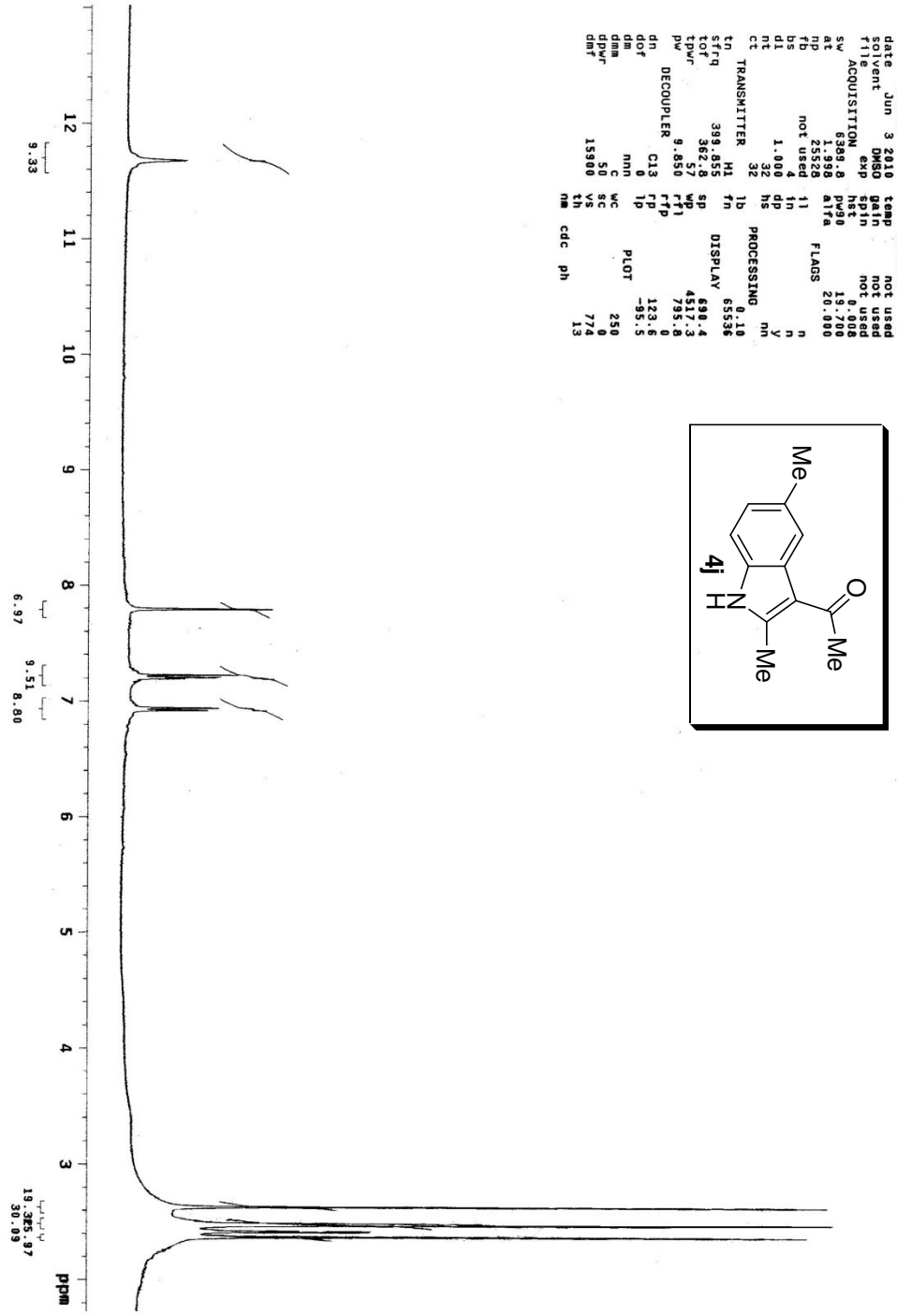
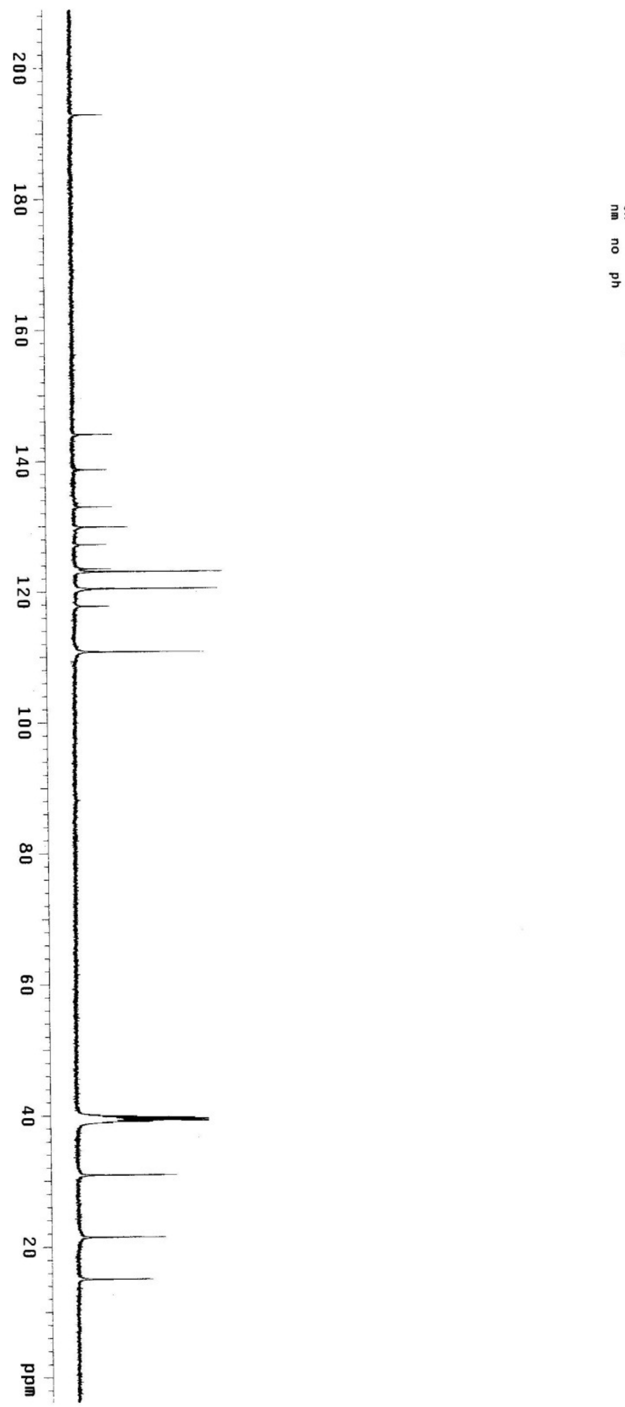
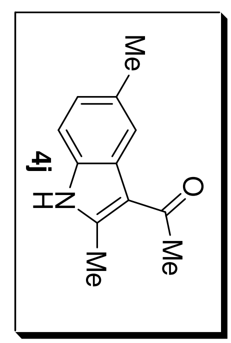
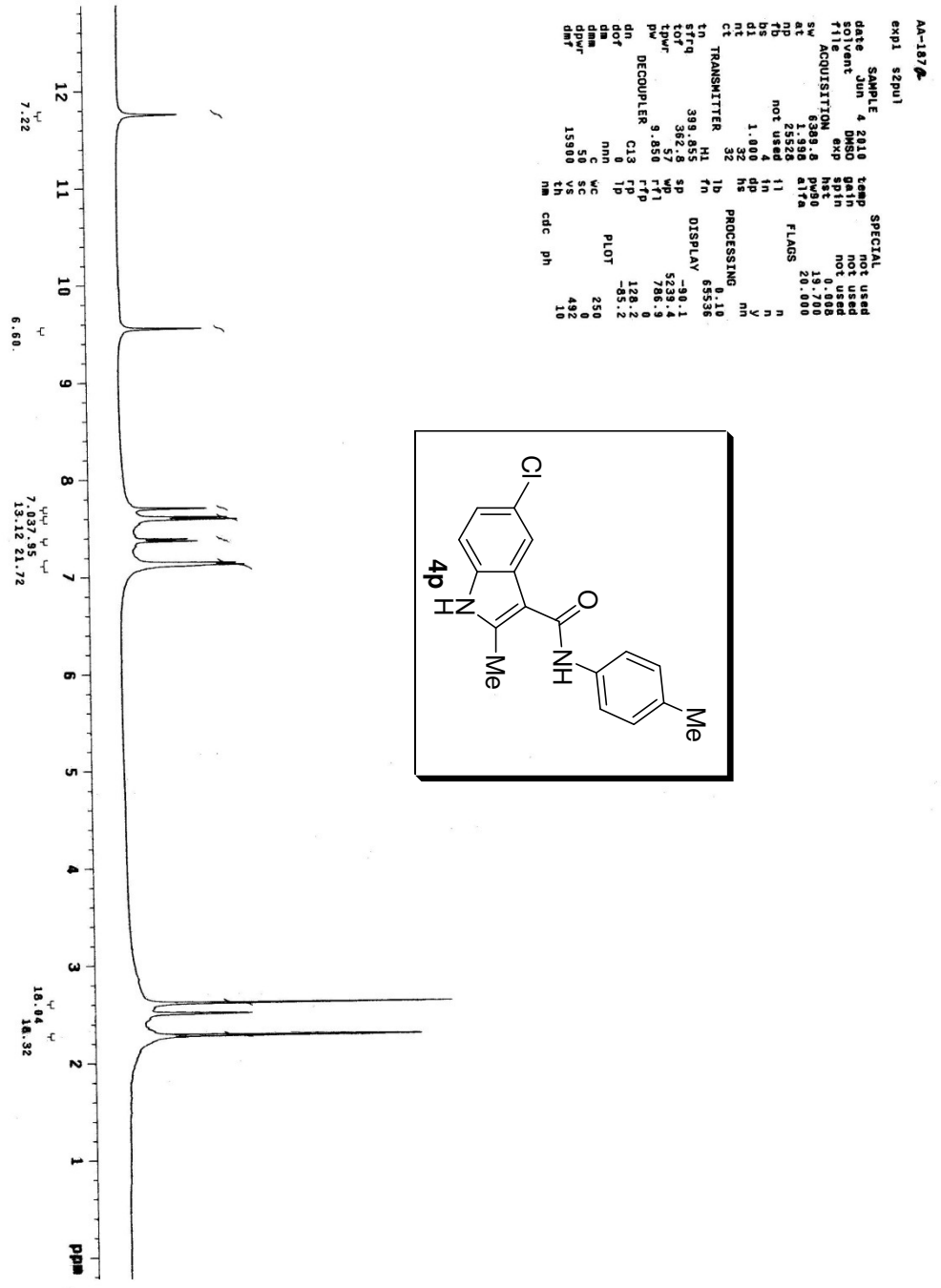


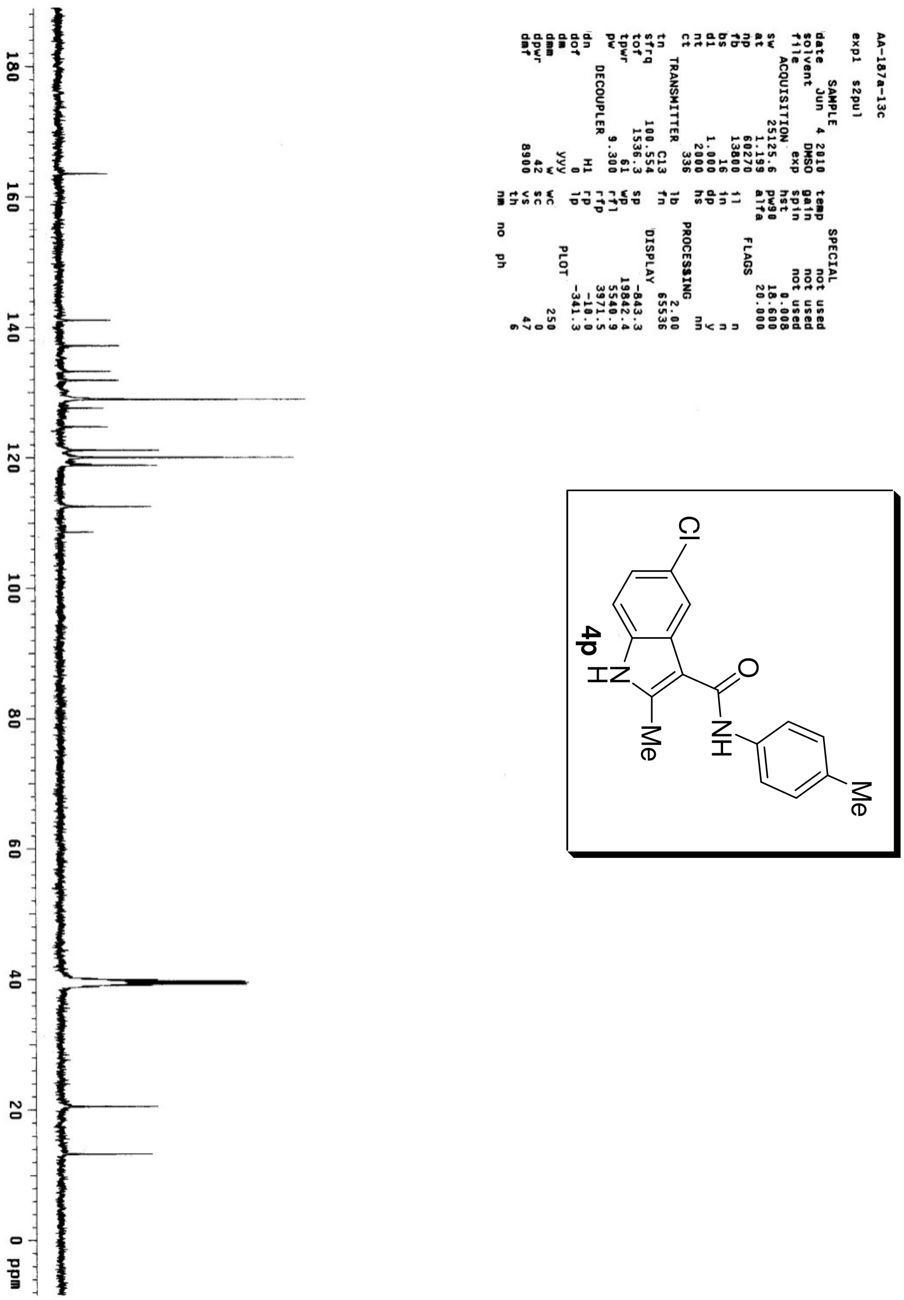












Chapter IV

Pd(II)-Catalyzed One-pot Conversion of Aldehydes to Amides

Synthesis of primary amides is one of the most important processes because of their utilization in a wide range of applications in academia and industry, especially as intermediates in organic synthesis, raw material for plastics, detergents, lubricants and pharmaceuticals.[1] The primary amide is one of the key functional groups in some of the very important drug molecules such as Vindesine, an anticancer drug, and Saquinavir, a HIV protease inhibitor (Figure 1).[2] It also exhibits various biological activities such as antitumor,[3a] antibacterial,[3b] antiviral,[3c] immunosuppressants,[3d] HIV-reverse transcriptase inhibitors,[3e] hepatitis C virus NS3 protease inhibitors,[3f] cathepsin K inhibitors,[3g] neuronal nitric oxide synthase inhibitors[3h] and asparaginyl endopeptidases inhibitors.[3i-j] Therefore, the synthesis of primary amide functional group is one of the most important and useful processes in synthetic organic chemistry.

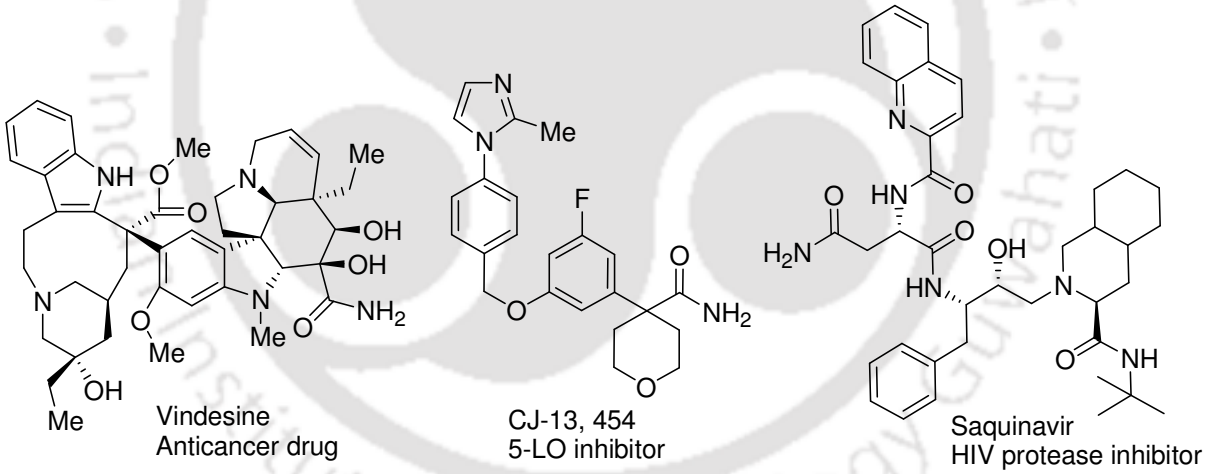
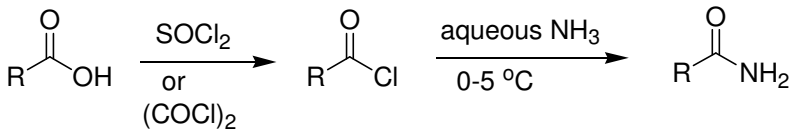


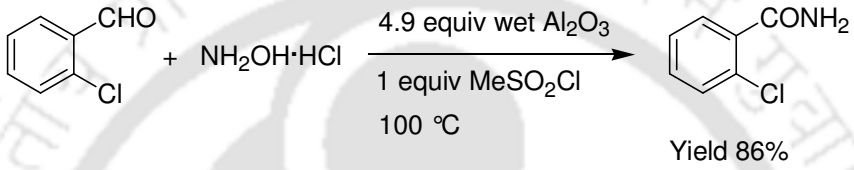
Figure 1 Some Biologically Active Primary Amides

The classical method used for the synthesis of primary amide functional group is conversion of acids to acid chlorides followed by treatment with aqueous ammonia under ice cool condition (Scheme 1).[4]



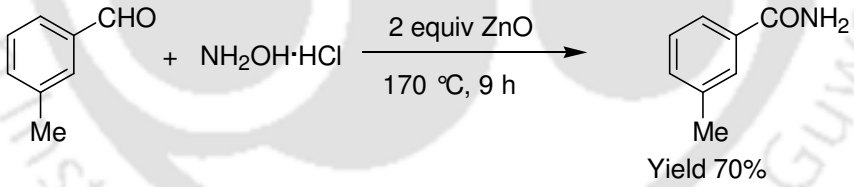
. ***Scheme 1***

The other important method for the synthesis of primary amides is conversion of aldoxime or aldehydes and hydroxylamine to amides in the presence of stoichiometric reagents such as acids or Lewis acids. For examples Sharghi and Sarvari have reported one-pot synthesis of primary amides from aldehydes in the presence of hydroxylamine hydrochloride, $MeSO_2Cl$ and excess wet-alumina at 100 ˚C (Scheme 2).[5a] Under these conditions a variety of aromatic and heteroaromatic aldehydes are converted to the corresponding amides.



Scheme 2

A similar procedure was also reported by Sharghi and Hosseini for the conversion of aldehydes to primary amides (Scheme 3).[5b] Unlike the previous method, this procedure involves the use of ZnO and excess amount of hydroxylamine hydrochloride at 140-170 ˚C.

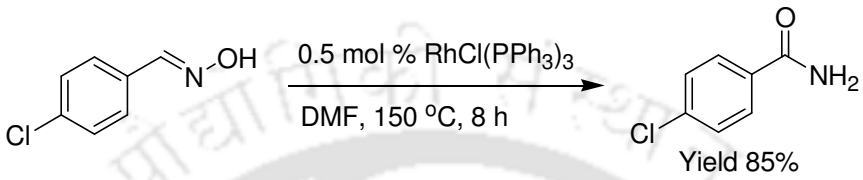


Scheme 3

However, these methods require stoichiometric or excess amount of the reagents which creates a waste disposal problem for large scale synthesis. To overcome these drawbacks, attention has been recently focused for the development of catalytic systems for the transformation of aldehydes in the presence of hydroxylamine or aldoxime to primary amides.[6]

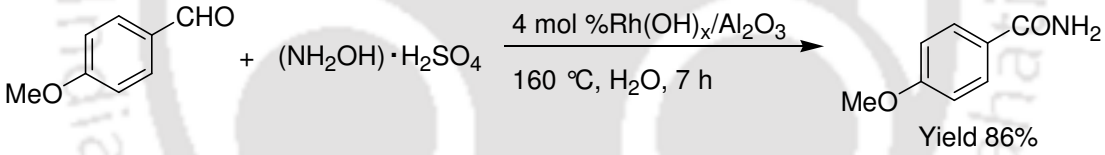
4.1 Transition-metal catalysts

Transition-metal-catalyzed methods have been developed for the conversion of aldoxime or aldehydes in the presence of hydroxylamine to give the primary amides in recent years. For examples, Chang and co-workers have used Wilkinson's complex to catalyze the one-pot transformation of aldoximes to amides with high selectivity (Scheme 4).[6a]



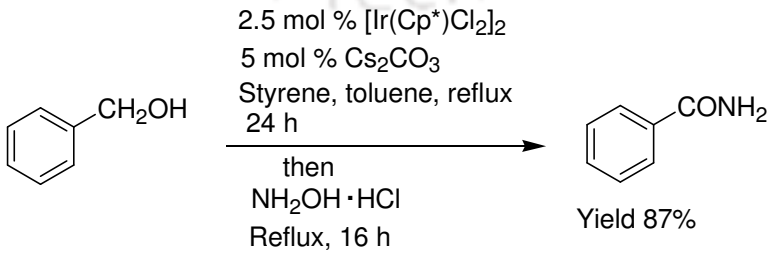
Scheme 4

$Rh(OH)_x/Al_2O_3$ has been used for the conversion of aldehydes to primary amides at 160 °C in autoclave (Scheme 5).[6b] The reaction is also equally effective for conversion of aldoximes to primary amides and a variety of aliphatic, aromatic and heteroaromatic aldehydes and aldoximes could be converted into primary amides in good yields.



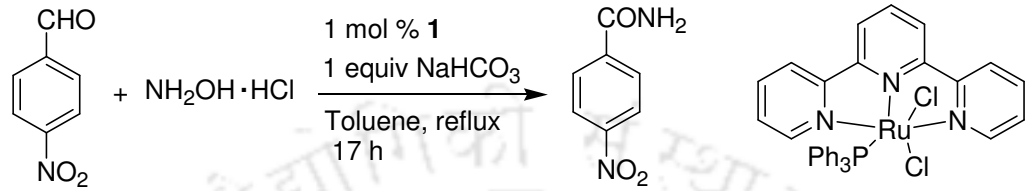
Scheme 5

Iridium catalyst, $\{Ir(Cp^*)Cl_2\}_2$ ($Cp^* = C_5Me_5$), has been studied for the synthesis of primary amides from alcohols in toluene under reflux in the presence of hydrogen acceptor (styrene) under inert atmosphere (Scheme 6).[6c] These conditions are also found to be efficient for the conversion of aldoximes to primary amides.



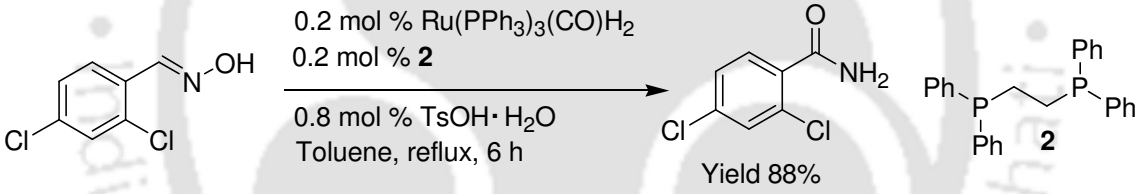
Scheme 6

Gnanamgari and Crabtree have employed (terpy)Ru(PPh_3)Cl_2 **1** for the conversion of aldehydes to primary amides in the presence of hydroxylamine hydrochloride and $NaHCO_3$ in refluxed toluene under inert atmosphere (Scheme 7). This catalytic system is also effective for conversion of aldoximes to primary amides.[6d]



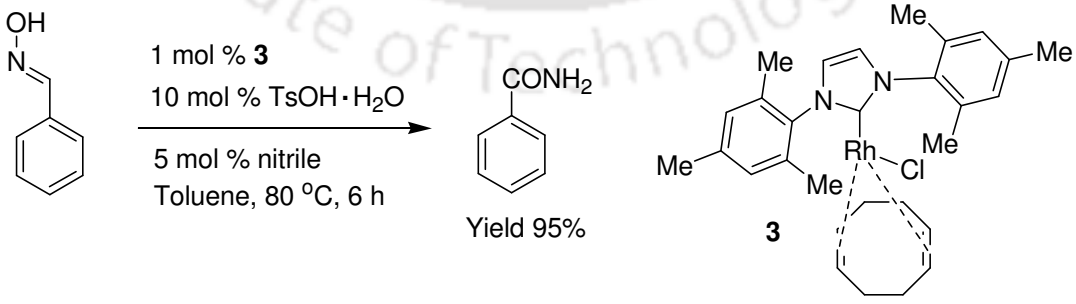
Scheme 7

Williams and co-workers have used Ru(PPh_3)$_3$(CO)H_2 for the conversion of aldoxime to primary amides in the presence of 1,2-bis(diphenylphosphino)ethane (dppe) **2** and toluenesulfonic acid hydrate (TsOH·H_2O) in toluene under reflux condition (Scheme 8).[6e]



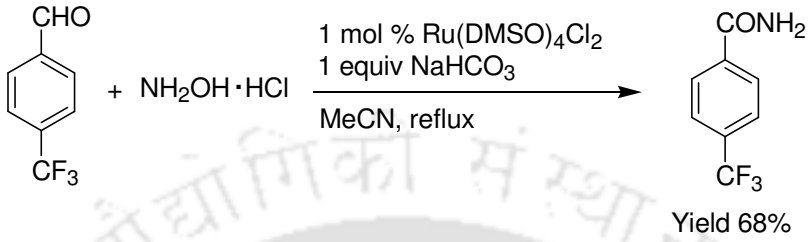
Scheme 8

Chang and co-workers have developed procedure for the formation of primary amides from aldoximes using Rh(cod)(IMes)Cl **3**, toluenesulfonic acid monohydrate (TsOH·H_2O), and a complementary nitrile in toluene at 80 ˚C (Scheme 9).[6f]



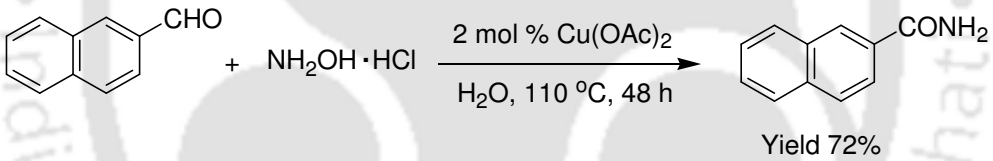
Scheme 9

$Ru(DMSO)_4Cl_2$ have been used for the one-pot conversion of aldehydes to primary amides in the presence of hydroxylamine hydrochloride and $NaHCO_3$ in refluxed acetonitrile under nitrogen atmosphere (Scheme 10).[6g]



Scheme 10

Martinez-Asencio and co-workers have used $Cu(OAc)_2$ as a catalyst for one-pot conversion of aldehydes to primary amides (Scheme 11).[6h] The reaction works well in water without addition of any ligands or bases and a variety of alkenyl aromatic and heteroaromatic aldehydes could be converted into primary amides in good yield.

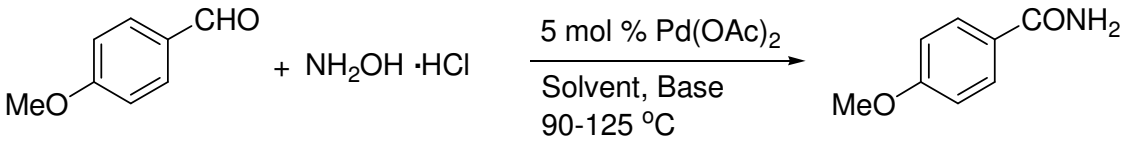


Scheme11

4.2 Present Study

In this chapter, we will describe the one-pot transformation of aldehydes with hydroxylamine hydrochloride to primary amides using $Pd(OAc)_2$ as a catalyst in aqueous DMSO at moderate temperature. First, the standardization of the protocol was carried out with 4-methoxybenzaldehyde as a model substrate using $Pd(OAc)_2$ in the presence of hydroxylamine hydrochloride in different solvents and bases at varied temperatures (Table 1). We were pleased to find that the reaction occurred efficiently to afford the desired 4-methoxybenzamide in 95% yield (100% conversion) when the substrate was stirred at 100 ^oC using 5 mol % of $Pd(OAc)_2$ in the presence of 1.2 equiv of Cs_2CO_3 in a 3:1

Table 1 The Standardisation of Reaction Conditions[a,b]



Entry	Solvent	Base	Temp (°C)	Time (h)	Yield (%)
1	DMSO	K_2CO_3	125	12	30
2	DMF	K_2CO_3	125	12	21
3	Toluene	K_2CO_3	125	12	12
4	DMSO:H_2O (9:1)	K_2CO_3	125	12	51
5	DMSO:H_2O (3:1)	K_2CO_3	125	12	90
6	DMSO:H_2O (1:1)	K_2CO_3	125	12	21
7	DMSO:H_2O (3:1)	KOH	125	10	14
8	DMSO:H_2O (3:1)	Cs_2CO_3	125	10	97
9	DMSO:H_2O (3:1)	Na_2CO_3	125	10	16
10	DMSO:H_2O (3:1)	$NaHCO_3$	125	10	14
11	DMSO:H_2O (3:1)	K_2CO_3	125	12	78[c]
12	DMSO:H_2O (3:1)	K_2CO_3	125	12	32[d]
13	DMSO:H_2O (3:1)	K_2CO_3	125	12	75[e]
14	DMSO:H_2O (3:1)	Cs_2CO_3	100	12	95
15	DMSO:H_2O (3:1)	K_2CO_3	100	12	13
16	DMSO:H_2O (3:1)	Cs_2CO_3	100	12	72[f]
17	DMSO:H_2O (3:1)	Cs_2CO_3	90	12	70
18	DMSO:H_2O (3:1)	Cs_2CO_3	100	8	14[g]

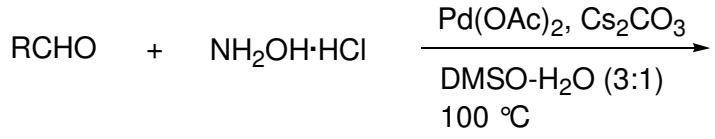
[a]To a stirred solution of *p*-methoxybenzaldehyde (0.5 mmol), $H_2NOH{\cdot}HCl$ (0.6 mmol) and base (0.6 mmol) in DMSO:H_2O (2 mL) for 5 h, $Pd(OAc)_2$ (5 mol %) was added and the reaction mixture was stirred for 5-7 h. [b]Isolated yield. [c]Base (1.5 equiv) was used. [d]$H_2NOH{\cdot}HCl$ (1 equiv) was used. [e]$H_2NOH{\cdot}HCl$ (1.5 equiv) was used. [f]$Pd(OAc)_2$ (2.5 mol%) was used. [g]$Pd(OAc)_2$ (5 mol %) was added at the beginning.

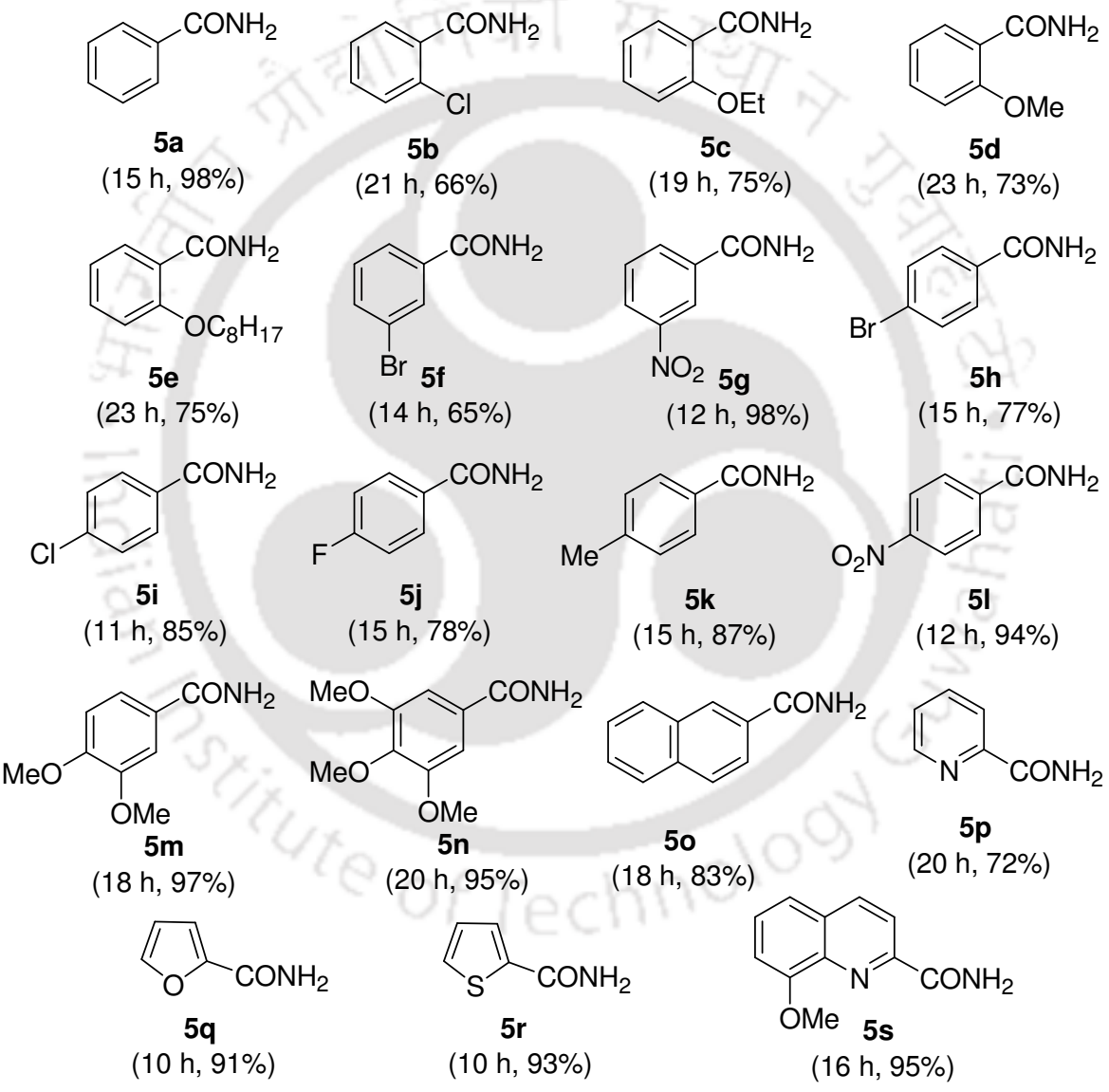
mixture of DMSO and H_2O (Table 1 entry 14). The ratio of DMSO and water was crucial for the outcome of the reaction. Pure organic solvents, DMSO, DMF and toluene, were found to be less effective providing the amide in <30% yields. Among the bases, $NaHCO_3$, Na_2CO_3, K_2CO_3 and Cs_2CO_3, the last provided the best results. Lowering of the reaction temperature (90 ^oC) or amount of the catalyst (2.5 mol %) led to the formation of the amide in 72% or 70% yields.

Next, the scope of the procedure was studied with respect to the reactions of aryl, alkyl and alkenyl aldehydes. The reaction of aryl aldehydes having 2-Cl, 2-OEt, 2-OMe, 2-OC_8H_{17}, 3-Br, 3-NO_2, 4-Br, 4-Cl, 4-F, 4-Me, 4-NO_2, 3,4-di-OMe and 3,4,5-tri-OMe substituents proceeded to give the respective primary amide in 65-98% yields (Table 2). Similar results were obtained with the reactions of 2-napthaldehyde and heteroaromatic aldehydes such as picolinaldehyde, furan-2-carbaldehyde, thiophene-2-carbaldehyde and 8-methoxyquinoline-2-carbaldehyde (Table 2). In addition, aliphatic aldehydes, acetaldehyde, *n*-hexanal, isobutyraldehyde, and cyclohexanecarbaldehyde and alkenyl aldehyde, cinnamaldehyde, were transformed to the corresponding primary amide in high yields (Table 3). These results suggest that the protocol is general and aryl, alkyl and alkenyl aldehydes can be transformed to the corresponding primary amides.

In these reactions, the aldehydes first undergo reaction with hydroxylamine hydrochloride in the presence of base to give aldoximes[7] that are transformed into amides by dehydration and hydration processes.[7e] For example, when a 1:1 mixture of benzaldehyde and benzonitrile was subjected to the optimized conditions, both the substrates were transformed into benzamide in 100% conversion and selectivity (Scheme 12). In contrast, the reaction of benzaldehyde with hydroxylamine hydrochloride in the presence of molecular sieve 3 Å in dry DMSO gave a trace of amide <5% along with benzonitrile (30%) and phenylaldoxime (65%) (Scheme 13). Moreover, the reactions are independent with respect to air or nitrogen atmosphere. Thus, the reaction of the aldehyde with hydroxylamine can give aldoxime which can undergo reaction with $Pd(OAc)_2$ to give intermediate ***a*** (Scheme 14). The latter can transform into ***c*** via ***b*** to complete the catalytic cycle by dehydration and hydration processes.

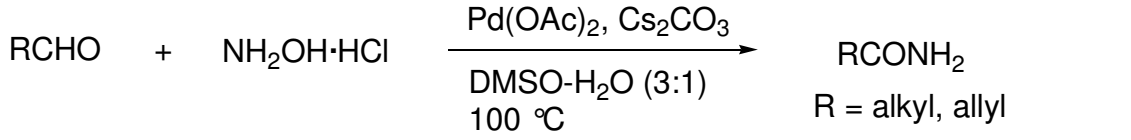
Table 2 Pd-Catalyzed Conversion of Aryl Aldehydes to Amides[a,b]

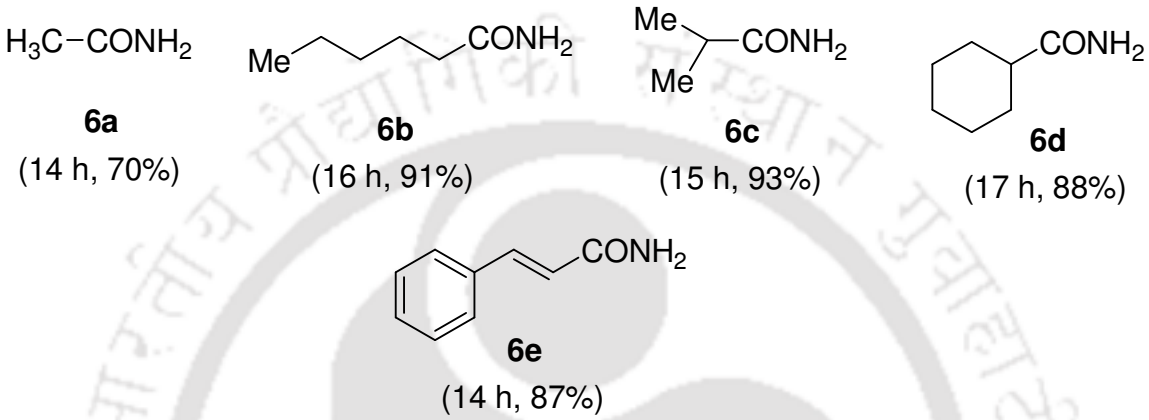




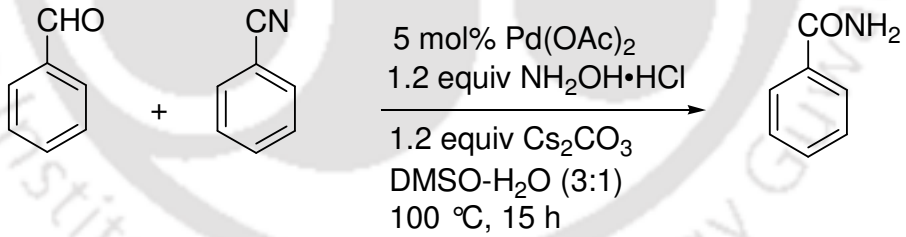
[a]To a stirred solution of aldehyde (0.5 mmol), $H_2NOH{\cdot}HCl$ (0.6 mmol) and Cs_2CO_3 (0.6 mmol) in DMSO:H_2O (3:1, 2 mL) at 100 °C for 5-7 h, $Pd(OAc)_2$ (5 mol %) was added and the reaction mixture was stirred for additional 5-19 h. [b]Isolated yield.

Table 3 Pd-Catalyzed Conversion of Alkyl and Allyl Aldehydes to Amides[a,b]

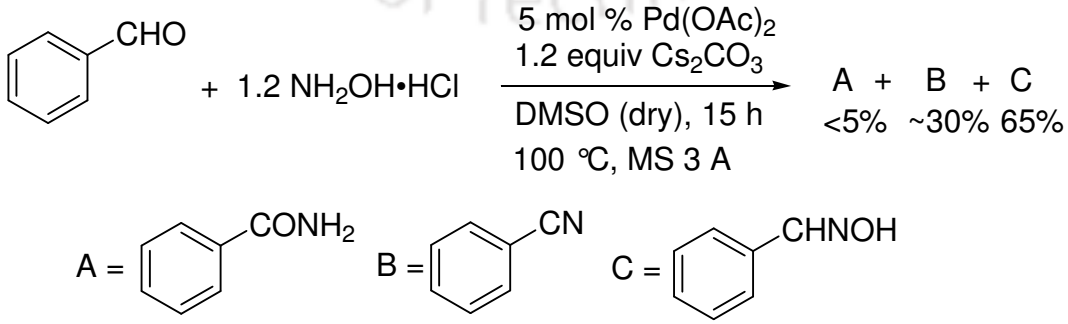




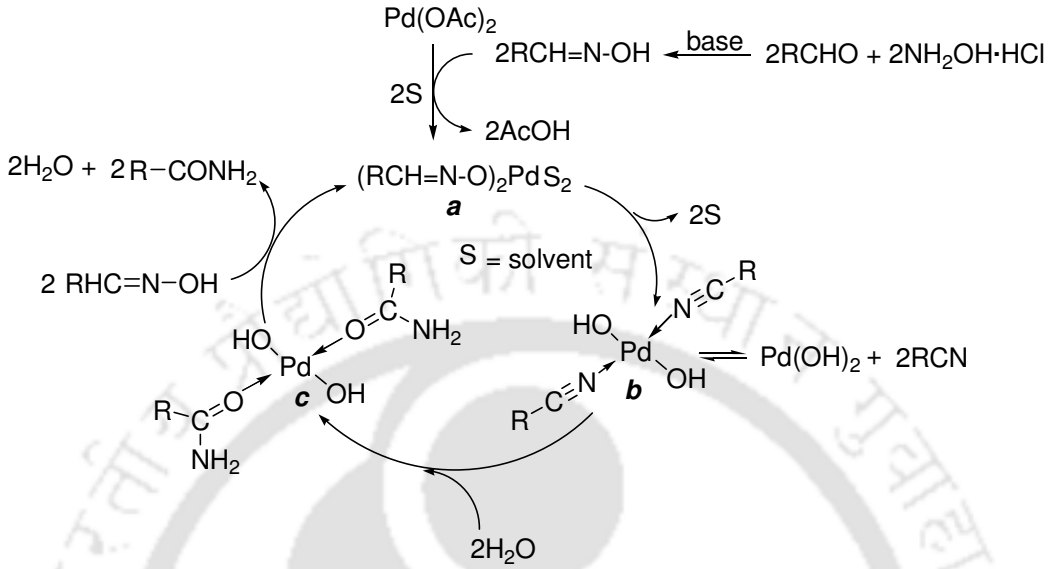
[a]To a stirred solution of aldehydes (0.5 mmol), $H_2NOH{\cdot}HCl$ (0.6 mmol) and Cs_2CO_3 (0.6 mmol) in DMSO:H_2O (3:1, 2 mL) at 100 °C for 5-7 h, $Pd(OAc)_2$ (5 mol %) was added and the reaction mixture was stirred for the additional 9-10 h. [b]Isolated yield.



Scheme 12



Scheme 13



Scheme 14

In conclusion, a simple, general and practical one-pot protocol is described for conversion of aryl, alkyl and alkenyl aldehydes into primary amides using $Pd(OAc)_2$ in DMSO and H_2O mixture under air. The reactions are selective and no by-product formation is observed.

Experimental Section

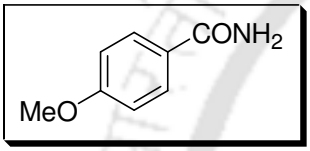
General Information

All chemicals were purchased from Aldrich and were used without further purification. ^{1}H NMR (400 MHz) and ^{13}C NMR (100 MHz) spectra were recorded with a Varian 400 spectrometer using TMS as an internal standard. Infrared (IR) spectra were recorded on a Perkin Elmer FT-IR spectrophotometer. Melting points were determined with a Büchi B-545 apparatus and are uncorrected. Elemental analyses were recorded with Perkin Elmer CHNS analyzer.

General Procedure for Pd-Catalyzed Conversion of Aldehydes to Primary Amides

Aldehyde (0.5 mmol), $NH_2OH{\cdot}HCl$ (0.6 mmol) and Cs_2CO_3 (0.6 mmol) were stirred at 100 ºC for 5-7 h in a 3:1 mixture of DMSO-H_2O (2 mL) under air. Then, $Pd(OAc)_2$ (5 mol %) was added and the stirring continued for the appropriate time. The progress of the reaction was monitored by TLC using ethyl acetate and hexane as eluent. After completion, the reaction mixture was cooled to room temperature and treated with water (1 mL). The resulting mixture was extracted with ethyl acetate (3 x 5 mL). Drying (Na_2SO_4) and evaporation of the solvent gave a residue that was purified by silica gel column chromatography using ethyl acetate and hexane.

Characterization Data of Products



4-Methoxybenzamide[6c] (Table 1)**:** 4-Methoxybenzaldehyde (68 mg, 0.5 mmol), $NH_2OH{\cdot}HCl$ (42 mg, 0.6 mmol) and Cs_2CO_3 (196 mg, 0.6 mmol) and $Pd(OAc)_2$ (5.6 mg, 5 mol %) were subjected to the reaction conditions described in the general procedure to afford the title compound as white solid in 95% (72 mg) yield.

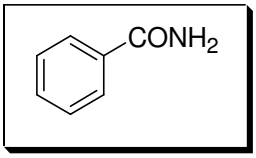
Mp: 166 °C (lit.[6c] mp 165-167 °C).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.78 (d, *J* = 9.2 Hz, 2H), 6.93 (d, *J* = 8.8 Hz, 2H), 5.85 (br s, 2H), 3.86 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 168.1, 161.3, 128.8, 125.5, 112.6, 54.6.

FT-IR (KBr): 3391, 3171, 1643, 1573, 1516, 1422, 1393, 1309, 1252, 1180, 1145, 1115, 1024 cm^{-1}.

Anal. Calcd. for $C_8H_9NO_2$: C, 63.56; H, 6.00; N, 9.27. Found: C, 63.62; H, 5.98; N, 9.23.



Benzamide[6c] (**5a**): Benzaldehyde (53 mg, 0.5 mmol), $NH_2OH{\cdot}HCl$ (42 mg, 0.6 mmol) and Cs_2CO_3 (196 mg, 0.6 mmol) and $Pd(OAc)_2$ (5.6 mg, 5 mol %) were subjected to the

reaction conditions described in the general procedure to afford the title compound as white solid in 98% (59 mg) yield.

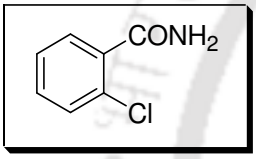
Mp: 127-128 °C (lit.[6c] 128-130 °C).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.79 (d, *J* = 7.6 Hz, 2H), 7.51 (t, *J* = 7.6 Hz, 1H), 7.43 (t, *J* = 7.6 Hz, 2H), 6.01 (br s, 2H).

^{13}C NMR (100 MHz, $CDCl_3$:DMSO-d_6 (3:1)): δ 168.8, 133.0, 130.6, 127.3, 126.7.

FT-IR (KBr): 3302, 3173, 3071, 2774, 1953, 1906, 1887, 1642, 1610, 1578, 1449, 1394, 1297, 1248, 1179, 1142, 1122, 1072, 1024 cm^{-1}.

Anal. Calcd. for C_7H_7NO: C, 69.41; H, 5.82; N, 11.56. Found: C, 69.47; H, 5.83; N, 11.59.



2-Chlorobenzamide[8a] (**5b**): 2-Chlorobenzaldehyde (70 mg, 0.5 mmol), $NH_2OH{\cdot}HCl$ (42 mg, 0.6 mmol) and Cs_2CO_3 (196 mg, 0.6 mmol) and $Pd(OAc)_2$ (5.6 mg, 5 mol %) were subjected to the reaction conditions described in the general procedure to afford the title compound as white solid in 66% (51 mg) yield.

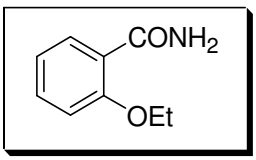
Mp: 140 °C (lit.[8a] 140-141 °C).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.76 (dd, *J* = 8.0, 1.2 Hz, 1H), 7.42-7.30 (m, 3H), 6.35 (br s, 1H), 6.22 (br s, 1H).

^{13}C NMR (100 MHz $CDCl_3$): δ 168.7, 134.1, 131.9, 131.0, 130.7, 130.6, 127.3.

FT-IR (KBr): 3362, 3181, 2923, 2853, 1961, 1932, 1821, 1651, 1632, 1566, 1481, 1432, 1403, 1262, 1119, 1047, 1037 cm^{-1}.

Anal. Calcd. for C_7H_6ClNO: C, 54.04; H, 3.89; N, 9.00. Found: C, 54.09; H, 3.87; N, 9.03.



2-Ethoxybenzamide (**5c**): 2-Ethoxybenzaldehyde (75 mg, 0.5 mmol), $NH_2OH{\cdot}HCl$ (42 mg, 0.6 mmol) and Cs_2CO_3 (196 mg, 0.6 mmol) and $Pd(OAc)_2$ (5.6 mg, 5 mol %) were subjected to the reaction conditions described in the general procedure to afford the title compound as white solid in 75% (62 mg) yield.

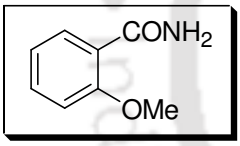
Mp: 131-132°C (lit.[8b] 132-134 °C).

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.19 (dd, *J* = 7.6, 2.0 Hz, 1H), 7.86 (br s, 1H), 7.43 (dt, *J* = 8.8, 1.6 Hz, 1H), 7.05 (t, *J* = 7.6 Hz, 1H), 6.94 (d, *J* = 8.0 Hz, 1H), 5.93 (br s, 1H), 4.18 (q, *J* = 7.2 Hz, 2H), 1.50 (t, *J* = 6.8 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 167.7, 157.4, 133.4, 132.5, 121.1, 120.9, 112.4, 64.8, 14.9.

FT-IR (KBr): 3371, 3177, 2986, 2930, 2877, 2774, 1961, 1923, 1883, 1645, 1597, 1493, 1471, 1449, 1404, 1393, 1287, 1242, 1171, 1119, 1038 cm^{-1}.

Anal. Calcd. for $C_9H_{11}NO_2$: C, 65.44; H, 6.71; N, 8.48. Found: C, 65.47; H, 6.70; N, 8.45.



2-Methoxybenzamide[8a] (**5d**): 2-Methoxybenzaldehyde (68 mg, 0.5 mmol), $NH_2OH{\cdot}HCl$ (42 mg, 0.6 mmol) and Cs_2CO_3 (196 mg, 0.6 mmol) and $Pd(OAc)_2$ (5.6 mg, 5 mol %) were subjected to the reaction conditions described in the general procedure to afford the title compound as white solid in 73% (55 mg) yield.

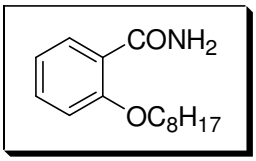
Mp: 127 °C (lit.[8a] 127-128 °C).

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.19 (dd, *J* = 8.0, 2.0 Hz, 1H), 7.69 (br s, 1H), 7.49-7.44 (m, 1H), 7.07 (dt, *J* = 7.6, 0.8 Hz, 1H), 6.98 (dd, *J* = 8.4, 0.8 Hz, 1H), 5.82 (br s, 1H), 3.96 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 167.5, 158.0, 133.5, 132.6, 121.3, 120.9, 111.5, 56.0.

FT-IR (KBr): 3413, 3196, 3013, 2979, 2948, 2839, 2753, 2036, 1927, 1621, 1607, 1574, 1487, 1463, 1434, 1393, 1274, 1243, 1179, 1148, 1106, 1047, 1022 cm^{-1}.

Anal. Calcd. for $C_8H_9NO_2$: C, 63.56; H, 6.00; N, 9.27. Found: C, 64.02; H, 5.98; N 9.33.



2-Octyloxybenzamide (**5e**): 2-Octyloxybenzaldehyde (117 mg, 0.5 mmol), $NH_2OH{\cdot}HCl$ (42 mg, 0.6 mmol) and Cs_2CO_3 (196 mg, 0.6 mmol) and $Pd(OAc)_2$ (5.6 mg, 5 mol %) were subjected to the reaction conditions described in the general procedure to afford the title compound as white solid in 75% (94 mg) yield.

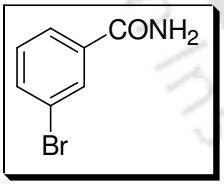
Mp: 60-61°C.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.18 (dd, *J* = 8.0, 1.6 Hz, 1H), 7.83 (br s, 1H), 7.40 (dt, *J* = 8.0, 1.6 Hz, 1H), 7.02 (t, *J* = 8.4 Hz, 1H), 6.93 (d, *J* = 8.4 Hz, 1H), 6.51 (br s, 1H), 4.08 (t, *J* = 6.8 Hz, 2H), 1.87-1.80 (m, 2H), 1.46-1.25 (m, 10H), 0.85 (t, *J* = 6.4 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 167.6, 157.6, 133.4, 132.6, 121.1, 121.0, 112.4, 69.3, 31.9, 29.4, 29.3, 26.2, 22.8, 14.2.

FT-IR (KBr): 3345, 3379, 3329, 3168, 2927, 2856, 1934, 1673, 1594, 1572, 1484, 1468, 1456, 1383, 1273, 1240, 1161, 1127, 1090, 1043, 1014, 994 cm^{-1}.

Anal. Calcd. for $C_{15}H_{23}NO_2$: C, 72.25; H, 9.30; N, 5.62. Found: C, 72.31; H, 9.28; N, 5.64.



3-Bromobenzamide[8c] (**5f**): 3-Bromobenzaldehyde (93 mg, 0.5 mmol), $NH_2OH{\cdot}HCl$ (42 mg, 0.6 mmol) and Cs_2CO_3 (196 mg, 0.6 mmol) and $Pd(OAc)_2$ (5.6 mg, 5 mol %) were subjected to the reaction conditions described in the general procedure to afford the title compound as white solid in 65% (65 mg) yield.

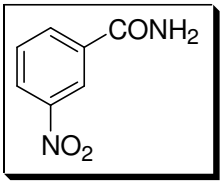
Mp: 154-155°C (lit.[8c] 155 °C).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.94 (t, *J* = 1.6, Hz, 1H), 7.72-7.69 (m, 1H), 7.65-7.63 (m, 1H), 7.31 (t, *J* = 8.0 Hz, 1H), 6.06 (br s, 1H), 5.93 (br s, 1H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 167.0, 135.3, 133.3, 129.9, 129.2, 125.6, 121.3.

FT-IR (KBr): 3352, 3176, 2922, 2840, 2780, 1950, 1660, 1621, 1565, 1427, 1392, 1259, 1149, 1124, 1067 cm^{-1}.

Anal. Calcd. for C_7H_6BrNO: C, 42.03; H, 3.02; N, 7.00. Found: C, 42.07; H, 3.01; N, 7.02.



3-Nitrobenzamide (**5g**): 3-Nitrobenzaldehyde (76 mg, 0.5 mmol), $NH_2OH{\cdot}HCl$ (42 mg, 0.6 mmol) and Cs_2CO_3 (196 mg, 0.6 mmol) and $Pd(OAc)_2$ (5.6 mg, 5 mol %) were subjected to the reaction conditions described in the general procedure to afford the title compound as light yellow solid in 98% (81 mg) yield.

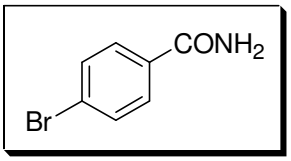
Mp: 141 °C (lit.[8d] 140-141 °C).

^1H NMR (400 MHz, $CDCl_3$): δ 8.64 (t, J = 1.6 Hz, 1H), 8.15-8.10 (m, 2H), 7.81 (br s, 1H), 7.45 (t, J = 7.6 Hz, 1H), 6.39 (br s, 1H).

^{13}C NMR (100 MHz, $CDCl_3$:DMSO-d_6, (3:1)): δ 166.6 147.5, 135.1, 133.5, 129.1, 125.5, 122.3.

FT-IR (KBr): 3449, 3335, 3175, 3093, 1706, 1690, 1624, 1528, 1412, 1393, 1350, 1126, 1100 cm^{-1}.

Anal. Calcd. for $C_7H_6N_2O_3$: C, 50.61; H, 3.64; N, 16.86. Found: C, 50.65; H, 3.62; N, 16.90.



4-Bromobenzamide[6c] (**5h**): 4-Bromobenzaldehyde (93 mg, 0.5 mmol), $NH_2OH{\cdot}HCl$ (42 mg, 0.6 mmol) and Cs_2CO_3 (196 mg, 0.6 mmol) and $Pd(OAc)_2$ (5.6 mg, 5 mol %) were subjected to the reaction conditions described in the general procedure to afford the title compound as white solid in 77% (77 mg) yield.

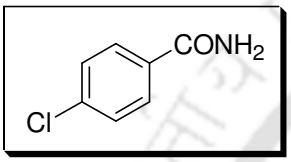
Mp: 198-199 °C (lit.[6c] 199-200 °C).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.66 (d, *J* = 8.8 Hz, 2H), 7.57 (d, *J* = 8.4 Hz, 2H), 6.01 (br s, 1H), 5.93 (br s, 1H).

^{13}C NMR (100 MHz, $CDCl_3$:DMSO-d_6, (1:1)): δ 167.5, 132.2, 130.5, 128.7, 125.0.

FT-IR (KBr): 3361, 3177, 2963, 2783, 1911, 1659, 1622, 1591, 1565, 1487, 1408, 1387, 1285, 1263, 1179, 1146, 1127, 1068, 1010 cm^{-1}.

Anal. Calcd. for C_7H_6BrNO: C, 42.03; H, 3.02; N, 7.00. Found: C, 42.08; H, 3.01; N, 7.03.



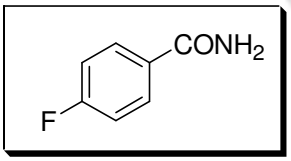
4-Chlorobenzamide[8e] (**5i**): 4-Chlorobenzaldehyde (70 mg, 0.5 mmol), $NH_2OH{\cdot}HCl$ (42 mg, 0.6 mmol) and Cs_2CO_3 (196 mg, 0.6 mmol) and $Pd(OAc)_2$ (5.6 mg, 5 mol %) were subjected to the reaction conditions described in the general procedure to afford the title compound as white solid in 87% (68 mg) yield.

Mp: 172-173 °C (lit.[8e] 172-174 °C).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.75 (d, *J* = 8.4 Hz, 2H), 7.43 (d, *J* = 8.8 Hz, 2H), 5.98 (br s, 2H). ^{13}C NMR (100 MHz, $CDCl_3$:DMSO-d_6 (3:1)): δ 167.9, 136.9, 131.9, 128.7, 127.9.

FT-IR (KBr): 3368, 3177, 1912, 1653, 1620, 1568, 1493, 1406, 1388, 1272, 1178, 1145, 1122, 1088 cm^{-1}.

Anal. Calcd. for C_7H_6ClNO: C, 54.04; H, 3.89; N, 9.00. Found: C, 54.08; H, 3.87; N, 9.04.



4-Fluorobenzamide[6c] (**5j**): 4-Fluorobenzaldehyde (62 mg, 0.5 mmol), $NH_2OH{\cdot}HCl$ (42 mg, 0.6 mmol) and Cs_2CO_3 (196 mg, 0.6 mmol) and $Pd(OAc)_2$ (5.6 mg, 5 mol %) were subjected to the reaction conditions described in the general procedure to afford the title compound as white solid in 78% (54 mg) yield.

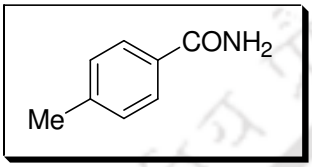
Mp: 153 °C (lit.[6c] 153-154 °C).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.83-7.79 (m, 2H), 7.13-7.10 (m, 2H), 5.93 (br s, 2H).

^{13}C NMR (100 MHz, $CDCl_3$:DMSO-d_6 (3:1)): δ 168.1, 129.8, 129.7, 114.9, 114.7.

FT-IR (KBr): 3332, 3165, 2791, 1668, 1600, 1589, 1513, 1416, 1398, 1296, 1226, 1158, 1123, 1097, 1037 cm^{-1}.

Anal. Calcd. for C_7H_6FNO: C, 60.43; H, 4.35; N, 10.07. Found: C, 60.47; H, 3.34; N, 10.04.



4-Methylbenzamide[6c] (**5k**): 4-Methylbenzaldehyde (60 mg, 0.5 mmol), $NH_2OH{\cdot}HCl$ (42 mg, 0.6 mmol) and Cs_2CO_3 (196 mg, 0.6 mmol) and $Pd(OAc)_2$ (5.6 mg, 5 mol %) were subjected to the reaction conditions described in the general procedure to afford the title compound as white solid in 87% (59 mg) yield.

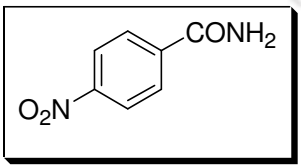
Mp: 161-162 °C (lit.[8f] 162-163 °C).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.71 (d, *J* = 8.0 Hz, 2H), 7.25 (d, *J* = 8.0 Hz, 2H), 6.06 (br s, 1H), 5.78 (br s, 1H), 2.41 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 168.9, 141.3, 130.5, 128.4, 127.1, 20.9.

FT-IR (KBr): 3343, 3165, 2918, 2785, 1922, 1667, 1615, 1569, 1413, 1397, 1286, 1262, 1188, 1144, 1123, 1108, 1020 cm^{-1}.

Anal. Calcd. for C_8H_9NO: C, 71.09; H, 6.71; N, 10.36. Found: C, 71.12; H, 6.72; N, 10.34.



4-Nitrobenzamide[6c] (**5l**): 4-Nitrobenzaldehyde (76 mg, 0.5 mmol), $NH_2OH{\cdot}HCl$ (42 mg, 0.6 mmol) and Cs_2CO_3 (196 mg, 0.6 mmol) and $Pd(OAc)_2$ (5.6 mg, 5 mol %) were subjected to the reaction conditions described in the general procedure to afford the title compound as light yellow solid in 94% (78 mg) yield.

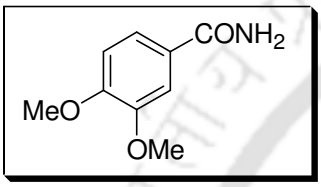
Mp: 199 °C (lit.[6c] 198-200 °C).

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.15 (d, *J* = 9.2 Hz, 2H), 7.96 (d, *J* = 8.8 Hz, 2H), 7.45 (br s, 1H), 6.31 (br s, 1H).

^{13}C NMR (100 MHz, $CDCl_3$:DMSO-d_6, (1:1)): δ 166.3, 148.5, 139.1, 128.2, 122.5.

FT-IR (KBr): 3361, 3177, 2963, 2783, 1911, 1659, 1622, 1591, 1565, 1487, 1408, 1387, 1285, 1263, 1179, 1146, 1127, 1068, 1010 cm^{-1}.

Anal. Calcd. for $C_7H_6N_2O_3$: C, 50.61; H, 3.64; N, 16.86. Found: C, 50.65; H, 3.63; N, 16.89.



3,4-Dimethoxybenzamide[8g] (**5m**): 3,4-Dimethoxylbenzaldehyde (83 mg, 0.5 mmol), $NH_2OH{\cdot}HCl$ (42 mg, 0.6 mmol) and Cs_2CO_3 (196 mg, 0.6 mmol) and $Pd(OAc)_2$ (5.6 mg, 5 mol %) were subjected to the reaction conditions described in the general procedure to afford the title compound as white solid in 97% (88 mg) yield.

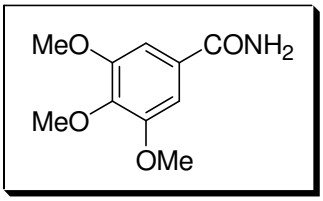
Mp: 67-68 °C (lit.[8g] 66-68 °C).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.43 (d, *J* = 2.0 Hz, 1H), 7.30 (dd, *J* = 8.4, 2 Hz, 1H), 6.85 (d, *J* = 8.4 Hz, 1H), 5.88 (br s, 2H), 3.91 (s, 6H).

^{13}C NMR (100 MHz, $CDCl_3$:DMSO-d_6 (3:1)): δ 168.6, 151.1, 147.9, 125.8, 120.4, 110.4, 109.7, 55.4.

FT-IR (KBr): 3371, 3175, 3008, 2960, 2937, 2847, 2773, 2606, 1849, 1651, 1620, 1599, 1578, 1518, 1463, 1455, 1422, 1382, 1342, 1275, 1262, 1239, 1180, 1145, 1123, 1034, 1014 cm^{-1}.

Anal. Calcd. for $C_9H_{11}NO_3$: C, 59.66; H, 6.12; N, 7.73. Found: C, 59.71; H, 6.11; N, 7.70.



3,4,5-Trimethoxybenzamide[8h] (**5n**): 3,4,5-Trimethoxylbenzaldehyde (98 mg, 0.5 mmol), $NH_2OH{\cdot}HCl$ (42 mg, 0.6 mmol) and Cs_2CO_3 (196 mg, 0.6 mmol) and $Pd(OAc)_2$ (5.6 mg, 5 mol %) were subjected to the reaction conditions described in the general procedure to afford the title compound as white solid in 97% (102 mg) yield.

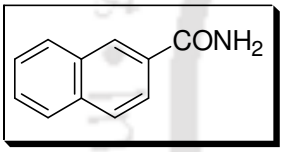
Mp: 173-174 °C (lit.[8h] 174-176 °C).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.03 (s, 2H), 6.10-5.80 (br s, 2H), 3.88 (s, 6H), 3.86 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$:DMSO-d_6 (3:1)): δ 168.3, 152.0, 139.7, 128.3, 104.4, 59.8, 55.4.

FT-IR (KBr): 3363, 3129, 2972, 2923, 2836, 2777, 2637, 1972, 1950, 1660, 1620, 1582, 1508, 1467, 1451, 1412, 1393, 1313, 1251, 1230, 1185, 1127, 1018, 994 cm^{-1}.

Anal. Calcd. for $C_{10}H_{13}NO_4$: C, 56.86; H, 6.20; N, 6.63. Found: C, 56.92; H, 6.19; N, 6.60.



2-Naphthamide[9a] (**5o**): 2-Naphthaldehyde (78 mg, 0.5 mmol), $NH_2OH{\cdot}HCl$ (42 mg, 0.6 mmol) and Cs_2CO_3 (196 mg, 0.6 mmol) and $Pd(OAc)_2$ (5.6 mg, 5 mol %) were subjected to the reaction conditions described in the general procedure to afford the title compound as white solid in 83% (71 mg) yield.

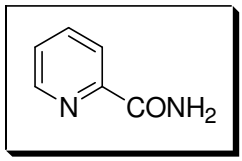
Mp: 192 °C (lit.[9a] 191-192 °C).

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.33 (s, 1H), 7.93-7.83 (m, 4H), 7.59-7.51 (m, 2H), 6.22 (br s, 1H), 5.77 (br s, 1H).

^{13}C NMR (100 MHz, $CDCl_3$:DMSO-d_6 (1:1)): δ 168.2, 133.6, 131.5, 130.4, 127.9, 127.2, 126.9, 126.6, 126.5, 125.6, 123.5.

FT-IR (KBr): 3377, 3196, 3054, 2743, 1954, 1825, 1653, 1632, 1611, 1574, 1405, 1363, 1260, 1143, 1115, 1097 cm^{-1}.

Anal. Calcd. for $C_{10}H_{11}NO$: C, 77.17; H, 5.30; N, 8.18. Found: C, 77.23; H, 5.31; N 8.15.



Pyridine-2-carboxamide[9b] (**5p**): Pyridine-2-carbaldehyde (54 mg, 0.5 mmol), $NH_2OH{\cdot}HCl$ (42 mg, 0.6 mmol) and Cs_2CO_3 (196 mg, 0.6 mmol) and $Pd(OAc)_2$ (5.6 mg, 5 mol %) were subjected to the reaction conditions described in the general procedure to afford the title compound as white solid in 72% (44 mg) yield.

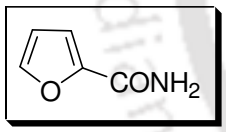
Mp: 104-105 °C (lit.[9b] 105-106 °C).

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.56 (d, *J* = 2.0 Hz, 1H), 8.18 (d, *J* = 7.6 Hz, 1H), 7.84 (dt, *J* = 7.6, 1.6 Hz, 2H), 7.45-7.42 (m, 1H), 5.73 (br s, 1H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 167.2, 149.8, 148.5, 137.4, 126.6, 122.6.

FT-IR (KBr): 3418, 3280, 3183, 2959, 2925, 2855, 2752, 1661, 1607, 1587, 1566, 1467, 1442, 1390, 1284, 1262, 1160, 1095, 1043, 996 cm^{-1}.

Anal. Calcd. for $C_6H_6N_2O$: C, 59.01; H, 4.95; N, 22.94. Found: C, 59.05; H, 4.94; N, 22.97.



Furan-2-carboxamide[6c] (**5q**): Furan-2-carbaldehyde (48 mg, 0.5 mmol), $NH_2OH{\cdot}HCl$ (42 mg, 0.6 mmol) and Cs_2CO_3 (196 mg, 0.6 mmol) and $Pd(OAc)_2$ (5.6 mg, 5 mol %) were subjected to the reaction conditions described in the general procedure to afford the title compound as white solid in 91% (51 mg) yield.

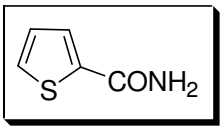
Mp: 140 °C (lit.[6c] 141-142 °C).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.44 (dd, *J* = 2.0, 0.8 Hz, 1H), 7.13 (dd, *J* = 3.6, 0.4 Hz, 1H), 6.49 (dd, *J* = 3.2, 1.6 Hz, 1H), 6.27 (br s, 1H), 6.12(br s, 1H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 160.5, 147.6, 144.6, 115.3, 112.5.

FT-IR (KBr): 3439, 3379, 3186, 2962, 2928, 2839, 2753, 1927, 1621, 1607, 1574, 1487, 1463, 1434, 1393, 1274, 1243, 1179, 1148, 1106, 1047, 1022 cm^{-1}.

Anal. Calcd. for $C_5H_5NO_2$: C, 54.05; H, 4.54; N, 12.61. Found: C, 54.09; H, 4.53; N, 12.57.



Thiophene-2-carboxamide[9c] (**5r**): Thiophene-2-carbaldehyde (56 mg, 0.5 mmol), $NH_2OH{\cdot}HCl$ (42 mg, 0.6 mmol) and Cs_2CO_3 (196 mg, 0.6 mmol) and $Pd(OAc)_2$ (5.6 mg, 5 mol %) were subjected to the reaction conditions described in the general procedure to afford the title compound as white solid in 93% (59 mg) yield.

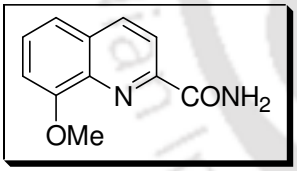
Mp: 178 °C (lit.[9d] mp 179-180 °C).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.51 (dd, *J* = 3.6, 1.2 Hz, 1H), 7.40 (dd, *J* = 5.2, 1.2 Hz, 1H), 6.99-6.97 (m, 1H), 6.27 (br s, 1H), 6.12 (br s, 1H).

^{13}C NMR (100 MHz, $CDCl_3$:DMSO-d_6, (3:1)): δ 163.4, 138.8, 129.9, 128.5, 127.1.

FT-IR (KBr): 3361, 3175, 2772, 1644, 1606, 1525, 1434, 1394, 1337, 1262, 1243, 1124, 1097, 1042 cm^{-1}.

Anal. Calcd. for C_5H_5NOS: C, 47.23; H, 3.96; N, 11.01; S, 25.22. Found: C, 47.27; H, 3.95; N, 10.98; S, 25.24.



8-Methoxyquiniline-2-carboxamide (**5s**): 8-Methoxyquiniline-2-carbaldehyde (94 mg, 0.5 mmol), $NH_2OH{\cdot}HCl$ (42 mg, 0.6 mmol) and Cs_2CO_3 (196 mg, 0.6 mmol) and $Pd(OAc)_2$ (5.6 mg, 5 mol %) were subjected to the reaction conditions described in the general procedure to afford the title compound as light yellow solid in 95% (96 mg) yield.

Mp: 159-160 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.28 (q, *J* = 8.4 Hz, 2H), 8.19 (br s, 1H), 7.53 (t, *J* = 8.4 Hz, 1H), 7.43 (dd, *J* = 8.4, 1.2 Hz, 1H), 7.08 (d, *J* = 7.6 Hz, 1H), 5.70 (br s, 1H), 4.07 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 167.4, 155.4, 148.4, 138.5, 137.3, 130.5, 128.5, 119.6, 119.5, 108.4, 56.0.

FT-IR (KBr): 3432, 3269, 3185, 2924, 2853, 1694, 1614, 1585, 1565, 1507, 1474, 1438, 1392, 1375, 1324, 1266, 1200, 1175, 1131, 1101, 1017, 994 cm^{-1}.

Anal. Calcd. for $C_{11}H_{10}N_2O_2$: C, 65.34; H, 4.98; N, 13.85. Found: C, 65.36; H, 4.97; N, 13.87.

Acetamide (**6a**): Acetaldehyde (22 mg, 0.5 mmol), $NH_2OH{\cdot}HCl$ (42 mg, 0.6 mmol) and Cs_2CO_3 (196 mg, 0.6 mmol) and $Pd(OAc)_2$ (5.6 mg, 5 mol %) were subjected to the reaction conditions described in the general procedure to afford the title compound as white solid in 70% (21 mg) yield.

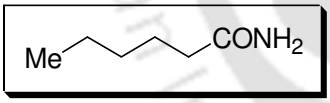
Mp: 80-81 °C (lit.[9e] 81 °C).

^1H NMR ($CDCl_3$, 400 MHz): δ 6.28 (br s, 1H), 6.11 (br s, 1H), 2.00 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$:DMSO-d_6, (3:1)): δ 173.8, 22.3.

FT-IR (KBr): 3419, 3214, 2791, 1661, 1613, 1434, 1397, 1352, 1133, 1048, 1004 cm^{-1}.

Anal. Calcd. for C_2H_5NO: C, 40.67; H, 8.53; N, 23.71. Found: C, 40.69; H, 8.51; N, 23.68.



Hexanamide[9f] (**6b**): Hexanaldehyde (50 mg, 0.5 mmol), $NH_2OH{\cdot}HCl$ (42 mg, 0.6 mmol) and Cs_2CO_3 (196 mg, 0.6 mmol) and $Pd(OAc)_2$ (5.6 mg, 5 mol %) were subjected to the reaction conditions described in the general procedure to afford the title compound as white solid in 91% (52 mg) yield.

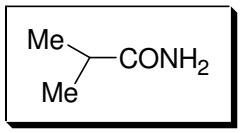
Mp: 101-102 °C (lit.[9f] 100-102 °C).

^1H NMR ($CDCl_3$, 400 MHz): δ 6.00 (br s, 1H), 5.60 (br s, 1H), 2.17 (t, J = 7.6 Hz, 2H), 1.63-1.55 (m, 2H), 1.29-1.26 (m, 4H), 0.87-0.84 (m, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 176.6, 36.0, 31.5, 25.3, 22.4, 14.0.

FT-IR (KBr): 3367, 3199, 2950, 2936, 2869, 2807, 1654, 1635, 1456, 1425, 1412, 1377, 1338, 1291, 1264, 1228, 1140, 1108 cm^{-1}.

Anal. Calcd. for $C_6H_{13}NO$: C, 62.57; H, 11.38; N, 12.16. Found: C, 62.62; H, 11.39; N, 12.12.



Isobutyramide[9g] (**6c**): Isobutyraldehyde (36 mg, 0.5 mmol), $NH_2OH{\cdot}HCl$ (42 mg, 0.6 mmol) and Cs_2CO_3 (196 mg, 0.6 mmol) and $Pd(OAc)_2$ (5.6 mg, 5 mol %) were subjected to the reaction conditions described in the general procedure to afford the title compound as white solid in 93% (41 mg) yield.

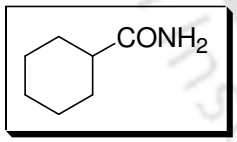
Mp: 129-130°C (lit.[9g] 128-130 °C).

^{1}H NMR ($CDCl_3$, 400 MHz): δ 5.41 (br s, 2H), 2.44-2.37 (m, 1H), 1.17 (s, 3H), 1.15 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 180.4, 35.1, 19.7.

FT-IR (KBr): 3360, 3187, 2970, 2932, 2870, 1645, 1635, 1471, 1456, 1429, 1360, 1296, 1170, 1147, 1090 cm^{-1}.

Anal. Calcd. for C_4H_9NO: C, 55.15; H, 10.41; N, 16.08. Found: C, 55.19; H, 10.40; N, 16.04.



Cyclohexanecarboxamide[9h] (**6d**): Cyclohexanecarbaldehyde (56 mg, 0.5 mmol), $NH_2OH{\cdot}HCl$ (42 mg, 0.6 mmol) and Cs_2CO_3 (196 mg, 0.6 mmol) and $Pd(OAc)_2$ (5.6 mg, 5 mol %) were subjected to the reaction conditions described in the general procedure to afford the title compound as white solid in 88% (56 mg) yield.

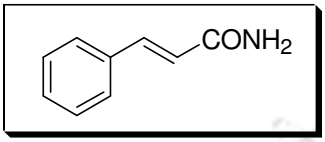
Mp: 186 °C (lit.[9h] 185-187 °C).

^{1}H NMR ($CDCl_3$, 400 MHz): δ 5.63 (br s, 1H), 5.47 (br s, 1H), 2.15-2.08 (m, 1H), 1.89-1.63 (m, 5H), 1.44-1.17 (m, 5H).

^{13}C NMR (100 MHz, $CDCl_3$:DMSO-d_6 (3:1)): δ 178.2, 43.4, 28.6, 24.8, 24.7.

FT-IR (KBr): 3345, 3174, 2928, 2852, 1665, 1634, 1445, 1430, 1356, 1345, 1286, 1230, 1154, 1037 cm^{-1}.

Anal. Calcd. for $C_7H_{13}NO$: C, 66.10; H, 10.30; N, 11.01. Found: C, 66.15; H, 10.31; N, 10.96.



Cinnamide[6e] (**6e**): Cinnamaldehyde (66 mg, 0.5 mmol), $NH_2OH{\cdot}HCl$ (42 mg, 0.6 mmol) and Cs_2CO_3 (196 mg, 0.6 mmol) and $Pd(OAc)_2$ (5.6 mg, 5 mol %) were subjected to the reaction conditions described in the general procedure to afford the title compound as white solid in 87% (64 mg) yield.

Mp: 149-150 °C (lit.[6e] 148-151 °C).

^1H NMR ($CDCl_3$, 400 MHz) δ 7.61 (d, *J* = 15.6 Hz, 1H), 7.47 (dd, *J* = 7.2, 3.6 Hz, 2H), 7.33 (t, *J* = 3.6 Hz, 3H), 6.45 (d, *J* = 15.6 Hz, 1H), 6.07 (br s, 1H), 5.87 (br s, 1H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 168.3, 141.7, 134.7, 129.7, 128.8, 127.9, 120.3.

FT-IR (KBr): 3374, 3171, 3028, 2924, 2853, 2769, 1945, 1876, 1661, 1633, 1607, 1577, 1492, 1449, 1398, 1314, 1287, 1246, 1200, 1135, 115, 968, 940 cm^{-1}.

Anal. Calcd. for C_9H_9NO: C, 73.54; H, 6.16; N, 9.52. Found: C, 73.61; H, 6.15; N, 9.49.

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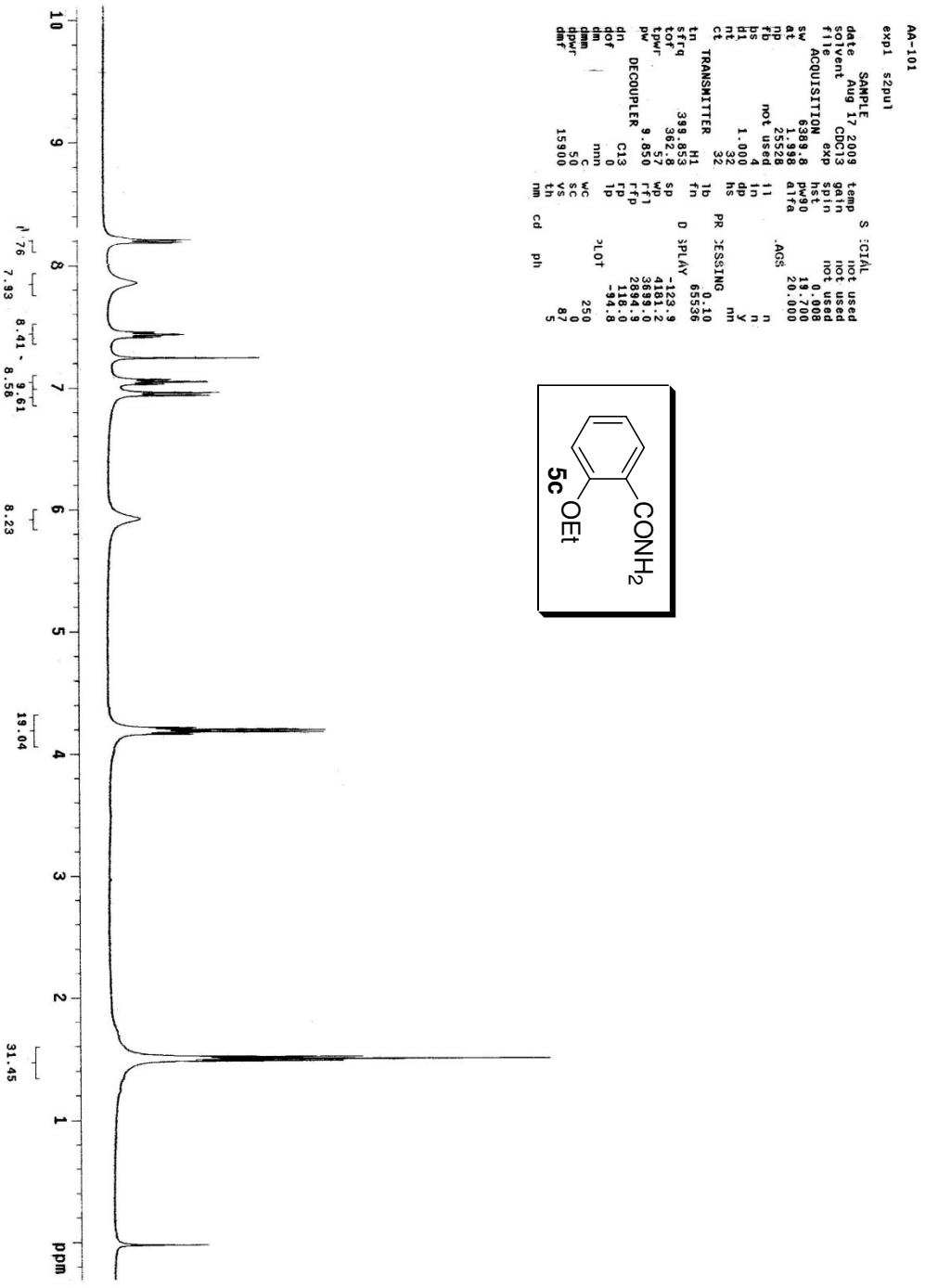

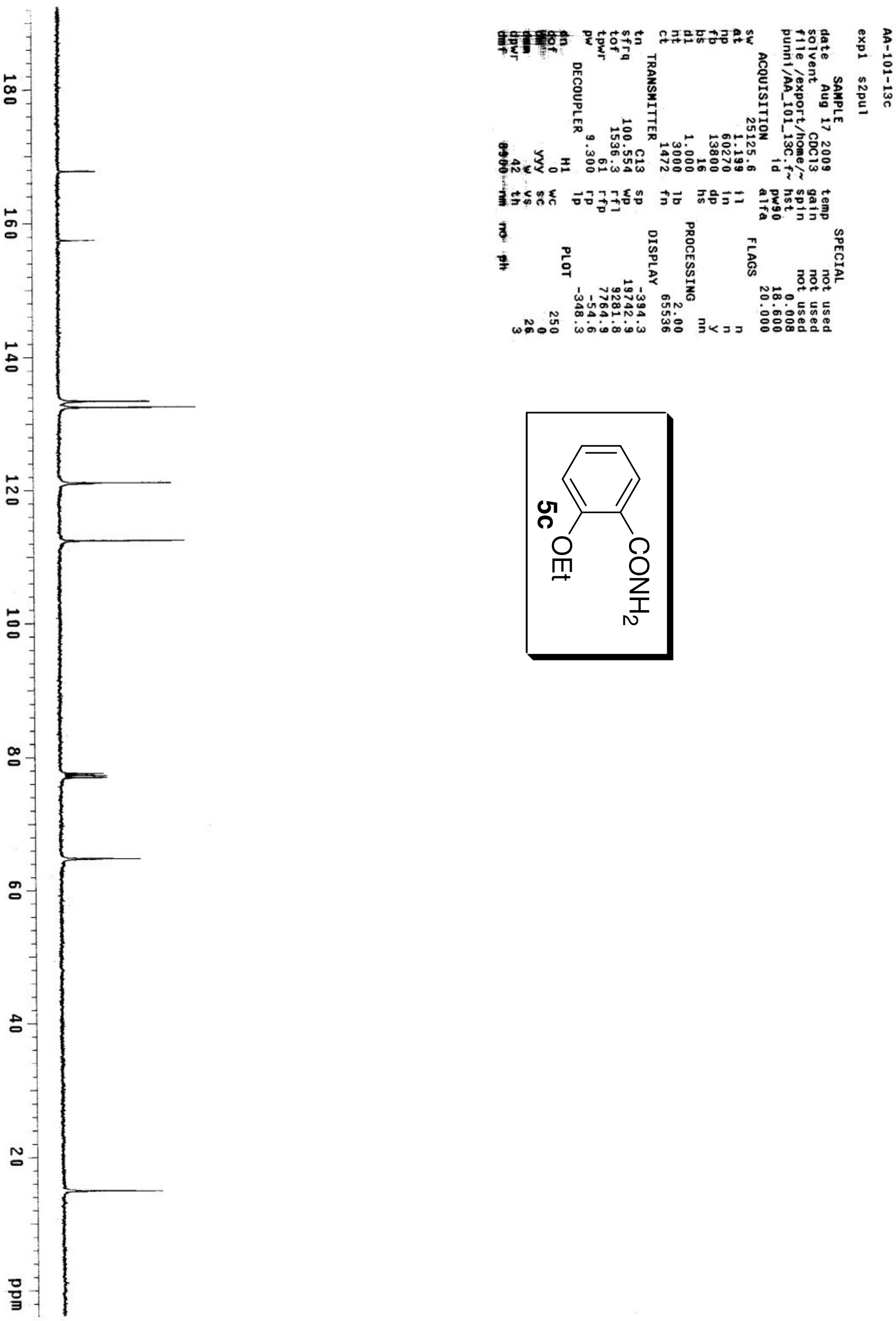

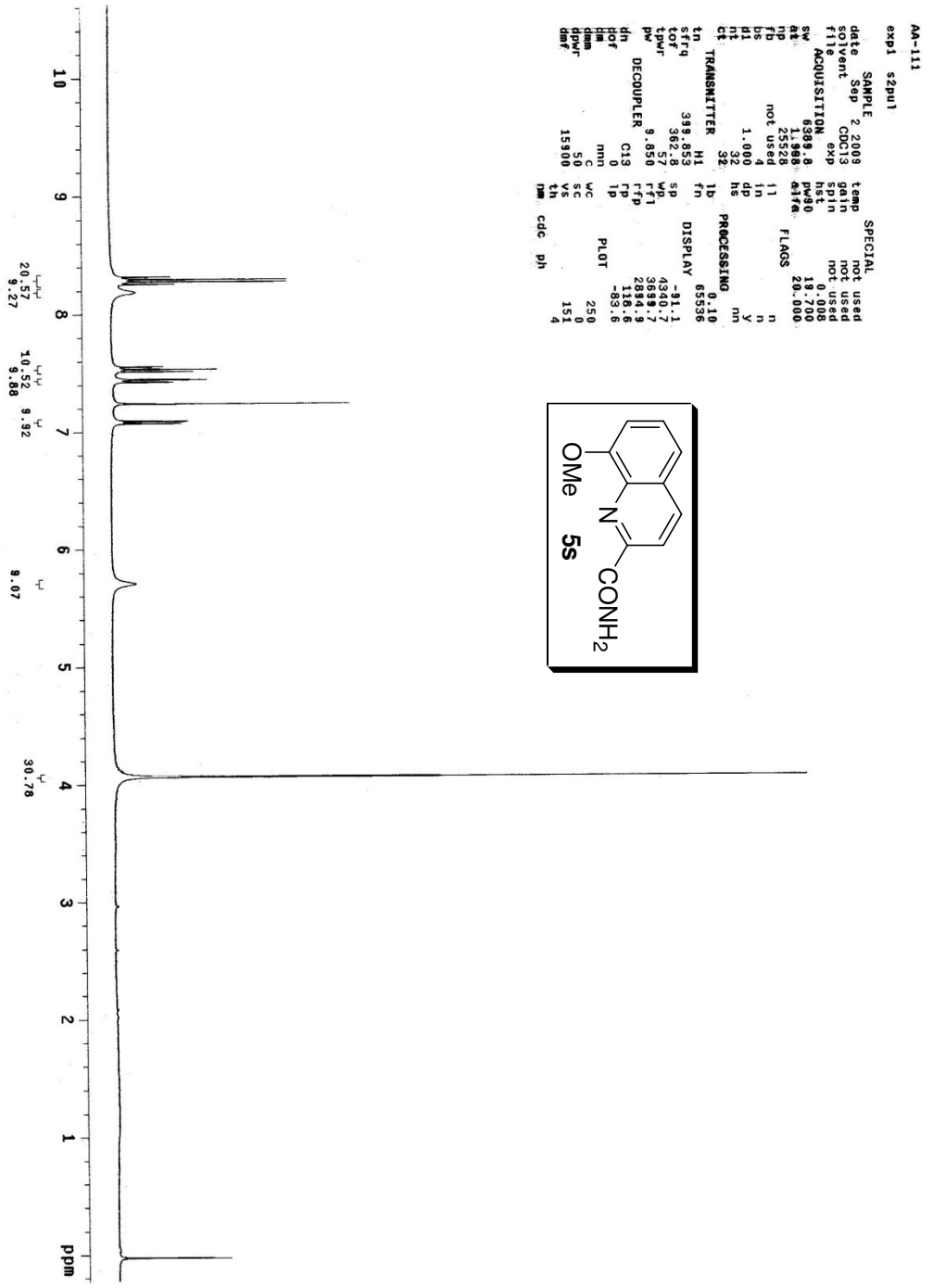

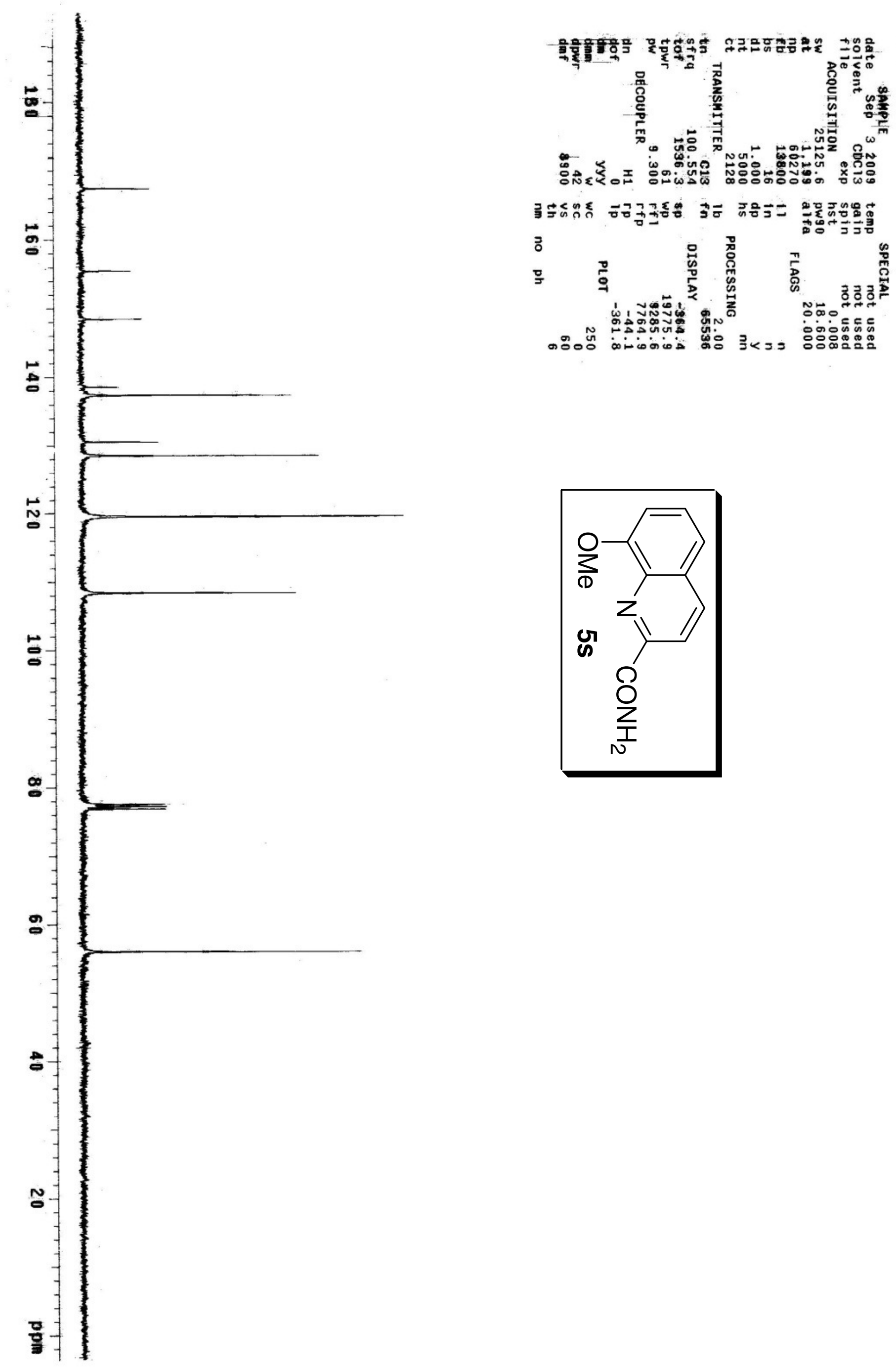

List of Publications

1. Ligand-Free Copper(II) Oxide Nanoparticles Catalyzed Synthesis of Substituted Benzoxazoles.
   Saha, P.; Ali, M. A.; Punniyamurthy, T. *Org. Synth*. **2011**, *88*, 398.

2. Copper-Mediated Synthesis of Substituted 2-Aryl-*N*-benzylbenzimidazoles and 2-Arylbenzoxazoles via *C-H* Functionalization/*C-N*/*C-O* Bond Formation.
   Guru, M. M.; Ali, M. A.; Punniyamurthy, T. *J. Org. Chem*. **2011**, *76*, 5295.

3. Pd-Catalyzed *C-H* Activation/*C-N* Bond Formation: A New Route to 1-Aryl-1*H*-benzotriazoles.
   Kumar, R. K.; Ali, M. A.; Punniyamurthy, T. *Org. Lett*. **2011**, *13*, 2102.

4. Copper(II)-Catalyzed Conversion of Bisaryloxime Ethers to 2-Arylbenzoxazoles via *C-H* Functionalization/*C-N*/*C-O* Bonds Formation.
   Guru, M. M.; Ali, M. A.; Punniyamurthy, T. *Org. Lett*. **2011**, *13*, 1194.

5. Domino Ligand-Free Copper-Catalyzed Synthesis of Polysubstituted Indoles.
   Ali, M. A.; Punniyamurthy, T. *Synlett* **2011**, 623.

6. Copper-Catalyzed Selective Hydroxylation of Aryl Halides with Tetrabutylammonium Hydroxide: Synthesis of Phenols and Alkyl Aryl Ethers.
   Paul, R.; Ali, M. A.; Punniyamurthy, T. *Synthesis* **2010**, 4268.

7. Cobalt-Catalyzed Intramolecular *C-N* and *C-O* Cross-Coupling Reactions: Synthesis of Benzimidazoles and Benzoxazoles.
   Saha, P.; Ali, M. A.; Ghosh, P.; Punniyamurthy, T. *Org. Biomol. Chem*. **2010**, *8*, 5692.

8. Pd-Catalyzed One-Pot Conversion of Aldehydes to Amides.
   Ali, M. A.; Punniyamurthy, T. *Adv. Synth. Catal*. **2010**, *355*, 288.

9. Efficient Copper Catalyzed *N*-Arylation of Amides and Imidazoles with Aryl Iodides.
   Ali, M. A.; Saha, P.; Punniyamurthy, T. *Synthesis* **2010**, 908.

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