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INVESTIGATION OF CATALYSTS FOR C-N COUPLING REACTIONS TO SYNTHESIZE PYRIDOIMIDAZOINDOLE, CARBAZOLE, AND CARBOLINE HETEROCYCLIC COMPOUNDS

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INTRODUCTION

1. The urgency of the dissertation

Molecules with aromatic heterocycles are ubiquitous in both life and the environment, finding wide-ranging applications in medicine, agriculture, and technology. Compounds featuring fused heterocyclic ring structures have found utility not only in organic semiconductor fields such as organic light-emitting diodes (OLEDs), organic photovoltaic cells (OPVs), and organic field-effect transistors (OFETs) but also in biomedicine, serving as biological sensors, cell staining agents, drug markers, diagnostic tools, and therapeutic agents. Imidazopyridines, nitrogen-containing heterocyclic compounds comprising an imidazole moiety fused with a pyridine ring, with imidazo[1,2-a]pyridine being the most significant derivative among imidazopyridines, exhibit intriguing biological activities such as antibacterial, antifungal, anti-inflammatory, antitumor, and antiviral properties. Some drugs belonging to this class are used in clinical treatments.

Carbazole, an aromatic polycyclic hydrocarbon consisting of two benzene rings flanking a pyrrole ring, hosts numerous carbazole alkaloid compounds in nature. Carbazole compounds possess structurally appealing features and diverse biological activities, including antioxidant, anti-inflammatory, antiviral, antitumor, antiepileptic, antipsychotic properties, as well as potential for diabetes treatment, garnering significant interest in the scientific community.

Carbolines, also known as pyridine indoles, can be categorized into four types based on the different positions of nitrogen atoms on the pyridine ring, namely α-carboline, β-carboline, γ-carboline, and δ-carboline. All four types of carbolines have been isolated from natural products, particularly β-carboline and γ-carboline, which have been extensively studied for their intriguing biological activities including anticancer, antimalarial, antibacterial, antifungal, and anti-parasitic properties. Furthermore, these compounds have found wide application in organic synthesis.

Due to the intriguing applications of the aforementioned structurally fused aromatic heterocyclic compounds, the research direction toward developing new synthetic methods for this structural type has garnered significant attention from scientists worldwide. Recently, methods for synthesizing fused and polyfused heterocyclic compounds using metal catalysts have been strongly developed. Among these, palladium catalysis has been and continues to be a focus of research, demonstrating important applications in organic synthesis. Recently, the use of readily available metals such as copper to replace the expensive palladium metal catalyst has been of interest to scientists. Therefore, we have chosen the topic

"Investigation of catalysts for C-N coupling reactions to synthesize pyridoimidazoindole, carbazole, and carboline heterocyclic compounds" with the aim of researching various catalyst systems based on palladium and copper using different organic ligands to synthesize heterocyclic compounds containing nitrogen heteroatoms through C-N coupling reactions.

2. Research objectives of the dissertation:

- To comprehensively study several catalyst systems based on palladium and copper using different organic ligands to synthesize heterocyclic compounds containing nitrogen heteroatoms through C-N coupling reactions.

3. Research content:

- Investigating the use of Pd catalyst systems with various organic ligands to synthesize pyridoimidazoindole fused heterocycles through double C-N coupling reactions and determining their chemical structures.

- Exploring the use of Cu catalyst systems with organic ligands to synthesize carbazole derivatives through double C-N coupling reactions and determining their chemical structures.

- Examining the use of Cu catalyst systems with organic ligands to synthesize β-carboline and δ-carboline derivatives *via* double C-N coupling reactions and elucidating their chemical structures.

CHAPTER 1. OVERVIEW

Chapter 1 comprises 28 pages, presenting an overview of the literature on nitrogen-containing heterocyclic compounds with indole structures and their biological activities; the published synthetic methods for synthesizing these compounds.

CHAPTER 2. RESEARCH METHODS AND EXPERIMENTS

Chapter 2 consists of 21 pages, providing detailed information on research methods, synthesis procedures, purification techniques, reaction yields, and physical properties of the synthesized compounds such as morphology, color, melting point, as well as comprehensive data of IR, ^{1}H NMR, ^{13}C NMR, HSQC, HMBC, and HRMS spectra.

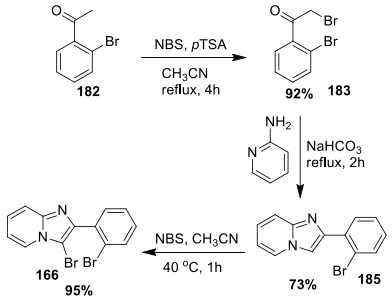
CHAPTER 3: RESULTS AND DISCUSSION

3.1. Synthesis of 5-aryl-5*H*-pyrido[2',1':2,3]imidazo[4,5-*b*]indole and 8-methyl-5-aryl-5*H*-pyrido[2',1':2,3]imidazo[4,5-*b*]indole

3.1.1. Synthesis of 5-aryl-5H-pyrido[2',1':2,3]imidazo[4,5-b]indole

The synthesis of intermediate **166** was carried out using the procedure reported by Kumar's group by cyclizing compound **183** with 2-aminopyridine, yielding a 73% yield [127]. Selective bromination at the position of compound 184 with iodine in pyridine at 50°C resulted in intermediate compound **166** (yield

95%). Subsequently, compound **166** underwent cyclization with various amines using a Pd-Cu catalyst system to yield the desired product **167** with high efficiency (Scheme 49).



Scheme 49. Synthesis of intermediate 2-(2-bromophenyl)-3-iodo-6-methylimidazo[1,2-a]pyridine (7)

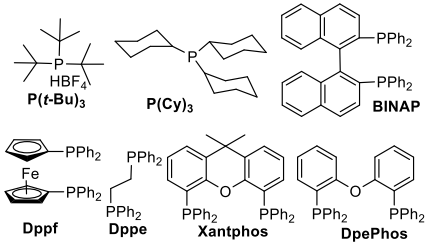
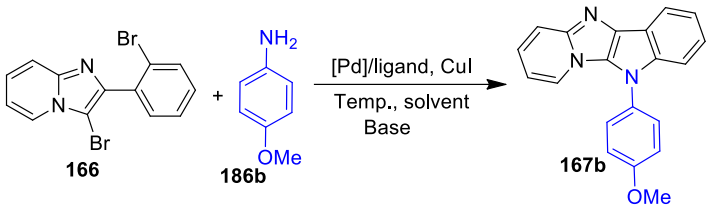


Figure 7. Structure of some bidentate ligands

To optimize this key reaction step, we chose the reaction of compound **166** with 4-methoxyaniline as the model reaction. According to the literature review, the use of bidentate ligands in combination with Pd catalysts yields good results for double C-N coupling reactions (Buchwald-Hartwig reaction). Therefore, we focused on investigating several bidentate ligands for this transformation (Figure 7). The standard conditions for the Buchwald-Hartwig reaction include a $Pd(OAc)_2$/BINAP catalyst system (10 mol%/10 mol%) and NaOtBu base in toluene solvent at reflux temperature (110°C) for 12 hours. The yield obtained under these conditions was quite low, only 25% (entry 1, Table 1). When combining $Pd_2(dba)_3$ catalyst with BINAP ligand (5 mol%/5 mol%), the synthesis yield increased to 41% (entry 2). However, combining $Pd_2(dba)_3$ with various bidentate ligands did not improve the synthesis of compound **167b**, as the yields were not high due to multiple side products from single coupling reactions. Based on the publication by Chauhan's group using Cu catalyst for C-N coupling reactions, we investigated the Pd/Cu dual catalyst system for this reaction (entries

3-5). It was observed that CuI combined with the $Pd_2(dba)_3$/BINAP catalyst system significantly increased the yield to 70% (entry 5). From this result, we further explored various bidentate ligands for the Pd/Cu catalyst system such as dppe, dppf, DpePhos, Xantphos (entries 6-9). The results showed that XantPhos was the most suitable ligand for the conversion efficiency, reaching 84% yield (entry 6). Some monodentate ligands commonly used for this type of reaction were also investigated, such as $PCy_3 \cdot HBF_4$ and $P(tBu)_3 \cdot HBF_4$, which only yielded trace amounts of the product (entries 10-11). Several bases and solvents were also investigated, but no improvement in reaction yield was observed (entries 12-17). Thus, the optimal conditions for synthesizing compound **167b** are as follows: $Pd_2(dba)_3$/CuI catalyst system (5 mol%/10 mol%), XantPhos ligand (10 mol%), NaOtBu base, toluene solvent, 110°C, 12 hours. The synthesis reaction achieved a yield of 84%.



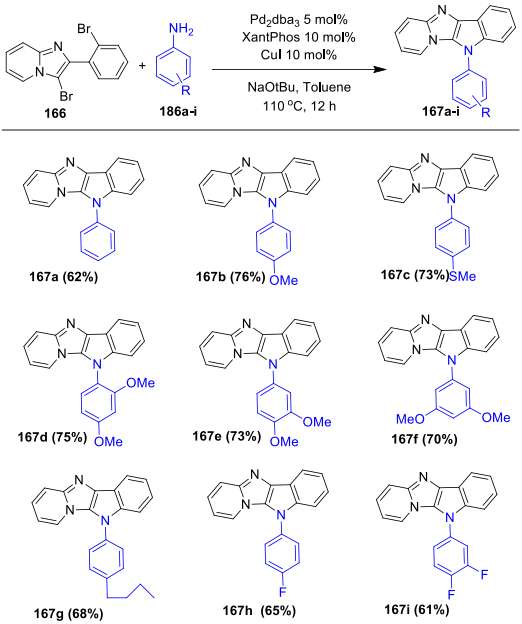
Scheme 50. Synthesis reaction of PIDI

Table 1. Optimization of PIDI synthesis reaction

Entry	Catalyst	Ligand	Co-catalyst	Base	Solvent	Time (h)	Temp. (°C)	Yield (%)[a]
1	$Pd(OAc)_2$	BINAP	-	NaOtBu	Toluene	12	110	25[b]
2	$Pd_2(dba)_3$	BINAP	-	NaOtBu	Toluene	12	110	41[b]
3	$Pd_2(dba)_3$	BINAP	CuI	NaOtBu	Toluene	12	110	70
4	$Pd_2(dba)_3$	BINAP	$Cu(OAc)_2$	NaOtBu	Toluene	12	110	67[b]
5	$Pd_2(dba)_3$	BINAP	CuI/1,10-phenanthroline	NaOtBu	Toluene	12	110	60[b]
6	**$Pd_2(dba)_3$**	**XantPhos**	**CuI**	**NaOtBu**	**Toluene**	**12**	**110**	**84**

7	$Pd_2(dba)_3$	DpePhos	CuI	NaOtBu	Toluene	12	110	46
8	$Pd_2(dba)_3$	Dppe	CuI	NaOtBu	Toluene	12	110	-
9	$Pd_2(dba)_3$	Dppf	CuI	NaOtBu	Toluene	12	110	25
10	$Pd_2(dba)_3$	$PCy_3 \cdot HBF_4$	CuI	NaOtBu	Toluene	12	110	-
11	$Pd_2(dba)_3$	$P(tBu)_3 \cdot HBF_4$	CuI	NaOtBu	Toluene	12	110	-
12	$Pd_2(dba)_3$	XantPhos	CuI	KOtBu	Toluene	12	110	53
13	$Pd_2(dba)_3$	XantPhos	CuI	Cs_2CO_3	Toluene	12	110	15
14	$Pd_2(dba)_3$	XantPhos	CuI	NaOtBu	1,4-Dioxane	12	110	34
15	$Pd_2(dba)_3$	XantPhos	CuI	NaOtBu	DMF	12	110	67
16	$Pd_2(dba)_3$	XantPhos	CuI	NaOtBu	Toluene	12	130	65
17	$Pd_2(dba)_3$	XantPhos	CuI	NaOtBu	Toluene	12	90	70

With the optimized results, we proceeded to expand the scope of the reaction by using various amines. The cyclized products **167a-i** were obtained with yields of up to 83% (Scheme 51). Amines containing electron-donating groups (OMe, SMe, nBu) exhibited higher yields compared to those containing electron-withdrawing groups (F). The structures of the synthesized compounds were confirmed using NMR and MS spectroscopic methods.



*Scheme 51. Synthesis reaction scheme of derivatives of 5-aryl-5H-pyrido[2',1':2,3]imidazo[4,5-b]indole **167***

Compound **167f** is a pale yellow crystalline solid with a melting point of 286-288°C. The ^{1}H-NMR spectrum of compound **167f** shows complete signals for all 17 protons presenting in the molecule. A singlet signal at 3.85 ppm, characteristic of the methoxy group proton, is observed. A doublet signal at 6.68 ppm with J = 2.3 Hz corresponds to the H-2' and H-6' protons, while a triplet signal at 6.59 ppm with J = 2.2 Hz is assigned to the H-4' proton of the 3,5-methoxyphenyl ring. A multiplet signal in the range of 8.17-8.11 ppm is attributed to the H-7 proton. Signals of the remaining aromatic protons resonate in the range of 7.89-6.74 ppm. In the ^{13}C NMR spectrum of compound **167f**, signals for all 21 carbon atoms present in the molecule are observed. Additionally, the high-resolution mass spectrum (HRMS) shows a peak at *m/z* 344.1399, corresponding to the $[M+H]^+$ ion of the molecular formula $C_{21}H_{17}N_3O_2$. Therefore, the structure of compound **167f** can be confirmed as expected.

Furthermore, the structural determination of compound **167f** (Figure 10) by single-crystal X-ray diffraction method confirms the structures of derivatives **167a-i** as expected.

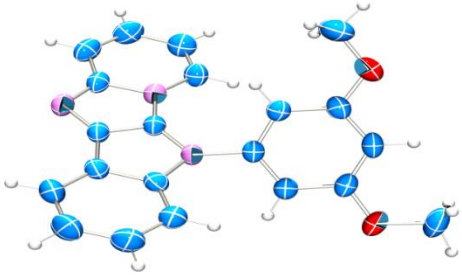


*Figure 10. Structure of compound **167f** (CCDC number 1874276) determined by single-crystal X-ray diffraction method*

From the experimental results in Table 1, we observed that the first C-N coupling reaction of compound **166** with various anilines predominantly occurs at the imidazo[1,2-*a*]pyridine ring due to the Pd coordination effect with the nitrogen atom in this ring, leading to the formation of multiple uncyclized by-products. Extending the reaction time to 24 hours did not improve the reaction yield. Therefore, we conclude that using a Pd catalyst for the second C-N coupling reaction does not yield the desired efficiency. To enhance the reaction efficiency, CuI was introduced into the reaction as a co-catalyst for the second C-N coupling cyclization step. With the participation of Cu co-catalyst, the reaction efficiency significantly increased (84%).

The proposed mechanism for the synthesis reaction of PIDI compound is illustrated in Figure 11. First, the oxidative addition of the Pd(0) catalyst to the starting material **166** forms intermediate Pd(II) complex A. Intermediate complex A undergoes ligand exchange reaction with the base NaOtBu to form intermediate complex B. Intermediate complex B reacts with the aniline derivative **186** to yield intermediate complex C. The reductive elimination of intermediate C generates intermediate **184** and regenerates the initial Pd(0) catalyst for the next Pd catalytic cycle. The mechanism of the second C-N coupling reaction is similar to the Buchwald-Hartwig reaction using Pd catalyst. CuI acts as a catalyst for the efficient intramolecular cyclization step, facilitating the formation of the C-N bond, specifically compound **184** forms a coordination bond with Cu(I) catalyst to form intermediate complex D. The intramolecular oxidative addition of complex D forms a Cu(III) ring complex (intermediate E). This intermediate E is unstable and readily undergoes reductive elimination to produce the cyclized PIDI product **167** and regenerate the Cu(I) catalyst for the next catalytic cycle.

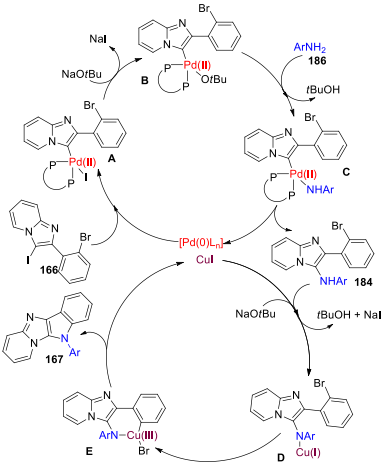
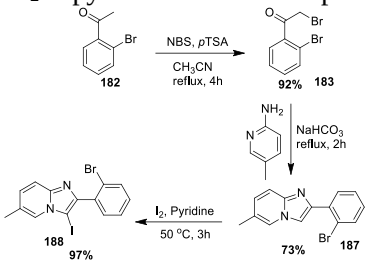


Figure 11. Proposed reaction mechanism using Pd-Cu catalyst system for PIDI synthesis reaction.

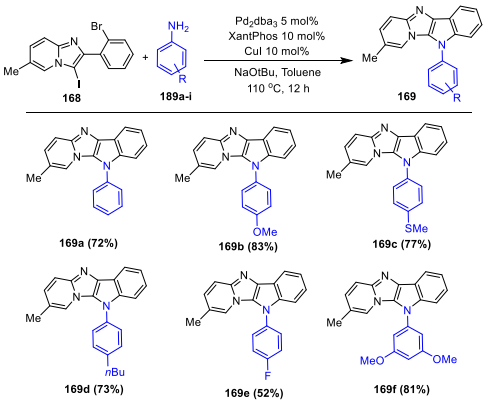
3.1.2. Synthesis of 8-methyl-5-aryl-5H-pyrido[2',1':2,3]imidazo[4,5-b]indole

Compound 2-(2-bromophenyl)-3-iodo-6-methylimidazo[1,2-*a*]pyridine **188** was synthesized *via* a two-step procedure outlined in Scheme 52. Compound **183** (obtained from the reaction between 2-bromoacetophenone **182** and NBS, followed by reaction with 2-amino-5-picoline to yield compound **187**, then cyclized by reaction with I_2 in pyridine to obtain compound **188**).



*Scheme 52. Synthesis of intermediate 2-(2-bromophenyl)-3-iodo-6-methylimidazo[1,2-a]pyridine (**7**).*

Applying the optimized conditions for synthesizing derivatives of 5-aryl-5*H*-pyrido[2',1':2,3]imidazo[4,5-*b*]indole **167** (section 3.3.1), derivatives of 8-methyl-5-aryl-5*H*-pyrido[2',1':2,3]imidazo[4,5-*b*]indole **169a-f** were synthesized according to Scheme 53. The structures of derivatives 8-methyl-5-aryl-5*H*-pyrido[2',1':2,3]imidazo[4,5-*b*]indole **169a-f** were determined by NMR and MS spectroscopy.



Scheme 53. Synthetic scheme of derivatives of 8-methyl-5-aryl-5H-pyrido[2',1':2,3]imidazo[4,5-b]indole.

In the ^{1}H-NMR spectrum of compound **169d**, a doublet signal appeared at 2.41 ppm with J = 1.1 Hz, characteristic of the methyl group proton. A strong singlet signal at 3.84 ppm was observed for the proton of the two methoxy groups. Multiplet signals in the range of 8.12-8.06 ppm were assigned to proton H-7. The remaining protons showed coalescence in the range of 7.78-6.54 ppm. In the ^{13}C NMR spectrum of compound **169d**, signals for all 22 carbon atoms present in the molecule were observed.

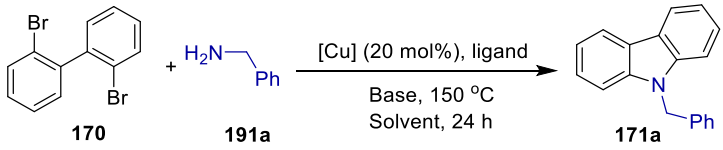
3.2. Synthesis of aryl, benzyl, and alkyl-substituted 9*H*-carbazole compounds

Given the potential applications of carbazole compounds, several methods have been developed for their synthesis, such as the C-N coupling reaction between 2,2'-dihalobiphenyl and amine using palladium catalysts, N-aryl hilation reaction between 2,2'-dihalobiphenyl and primary amine using palladium catalysts, and C-N coupling reaction using copper catalysts from diiodide and primary amine. However, a limitation of these methods is the expensive diiodide reagent. Therefore, developing new processes using readily available dibromide reagents in C-N coupling reactions catalyzed by copper with various types of amines is highly important. In this context, we have conducted research on the synthesis reaction of carbazole derivatives catalyzed by Cu from 2,2'-dibromobiphenyl and primary amine.

The reaction between 2,2'-dibromodiphenyl (**170**) and benzylamine (**191a**) was selected as the model reaction to investigate the optimal reaction conditions. The standard conditions for this reaction involved 1.5 equivalents of compound

2,2'-dibromodiphenyl (**170**), 3 equivalents of benzylamine (**191a**), 20 mol% CuI catalyst, and 24 mol% ligand at 150°C. Several key factors that could affect this cyclization process, including the catalyst, ligand, solvent, and temperature, were thoroughly examined.

When using CuI catalyst, K_2CO_3 base, and DMSO solvent (entries 1-6, Table 2), the highest synthesis efficiency of carbazole compound **171a** was achieved when using *L*-proline as the ligand (entry 6, Table 2). Subsequently, screening results for bases showed that the synthesis efficiency increased to 70% when using Cs_2CO_3 (entries 7-9). To investigate the influence of various copper catalysts on this transformation, several common copper salts including CuBr, CuCl, $CuCl_2$, $Cu(OAc)_2$, $Cu(OTf)_2$ were examined (entries 11-14). In practice, the product efficiency of carbazole **171a** increased to 72% when using CuCl as the catalyst. Among the solvents including *N*-methylpyrrolidone (NMP), DMF, toluene, dioxane tested under the same conditions (entries 15-18), DMF was found to be the most suitable solvent for this reaction (entry 16). Surprisingly, when testing with strong bases such as KOH, KOt-Bu (entries 19, 20), the synthesis efficiency of compound **171a** reached 81% when using KOH base at 150°C (entry 20) and 79% at 140°C (entry 21). Finally, when reducing the amount of CuCl and *L*-proline to 10 mol% and 12 mol%, respectively, while maintaining the reaction temperature at 140°C, the reaction still proceeded smoothly with an efficiency of 78% (entry 22). Therefore, the optimal reaction conditions for the synthesis of carbazole compound **171a** are as follows: 20 mol% CuCl, 12 mol% L-proline, KOH, 140°C, 24 hours.



*Scheme 54. Synthesis of carbazole compound **171a***

*Table 2. Optimization of the synthesis reaction of carbazole compound **171a***

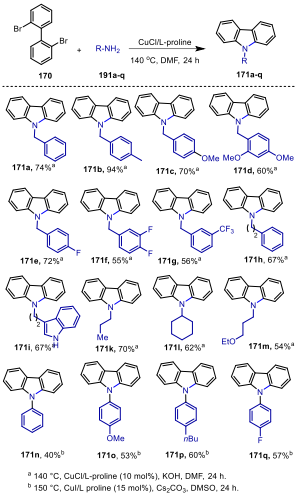
Entry	Catalyst	Ligand	Base	Solvent	Yield (%)[a]
1	CuI	BINAP	K_2CO_3	DMSO	25
2	CuI	Xantphos	K_2CO_3	DMSO	5
3	CuI	IPr.HCl	K_2CO_3	DMSO	8
4	CuI	1,10-phenanthroline	K_2CO_3	DMSO	15

5	CuI	bipyridine	K_2CO_3	DMSO	14
6	CuI	L-proline	K_2CO_3	DMSO	30
7	CuI	L-proline	K_3PO_4	DMSO	40
8	CuI	L-proline	KOAc	DMSO	14
9	CuI	L-proline	Cs_2CO_3	DMSO	70
10	CuCl	L-proline	Cs_2CO_3	DMSO	72
11	CuBr	L-proline	Cs_2CO_3	DMSO	34
12	$CuCl_2$	L-proline	Cs_2CO_3	DMSO	45
13	$Cu(OAc)_2$	L-proline	Cs_2CO_3	DMSO	52
14	$Cu(OTf)_2$	L-proline	Cs_2CO_3	DMSO	40
15	CuCl	L-proline	Cs_2CO_3	NMP	55
16	CuCl	L-proline	Cs_2CO_3	DMF	74
17	CuCl	L-proline	Cs_2CO_3	Toluene	56
18	CuCl	L-proline	Cs_2CO_3	Dioxane	48
19	CuCl	L-proline	KO*t*Bu	DMF	51
20	CuCl	L-proline	KOH	DMF	81
21	CuCl	L-proline	KOH	DMF	79[b]
22	**CuCl**	**L-proline**	**KOH**	**DMF**	**78[c]**

[a] **191a** (1.5 equiv.), Base (3 equiv.), [Cu] (20 mol%), phối tử (24 mol%), 150 °C, 24 h.

[b] **191a** (1.5 equiv.), Base (3 equiv.), [Cu] (20 mol%), phối tử (24 mol%), 140 °C, 24 h.

[c] **191a** (1.5 equiv.), Base (3 equiv.), [Cu] (10 mol%), phối tử (12 mol%), 140 °C, 24 h.



Scheme 55. Synthesis of derivatives of 9H-carbazole 171a-q

Based on the optimized reaction conditions, sixteen derivatives of carbazole **171a-q** were synthesized through the reaction between 2,2'-dibromodiphenyl (**170**) and amines **171a-q** with yields ranging from 40-94% (Scheme 55).

The substituent groups of the amines influence the synthesis efficiency of carbazole. Specifically, the reaction between 2,2'-dibromodiphenyl **170** and aliphatic amines (**191a-m**) yielded fairly good yields, especially for benzylamines containing electron-donating substituents (Me, MeO) with yields ranging from 70-94%. For benzylamines with electron-withdrawing substituents, the synthesis efficiency was only around 50-60%, possibly due to the weak nucleophilic nature of the amine. The reaction between **170** and other aliphatic amines **191i-m** resulted in the synthesis efficiency of carbazole **171i-m** ranging from 54-70%. The reaction between **170** and aniline derivatives (**191n-q**) under conditions using KOH base and 140°C yielded compounds **3n-q** with very low yields of only about 25-40%. When changing the reaction conditions to 150°C, 15 mol% CuI/L-proline, and Cs_2CO_3 base in DMSO solvent, the synthesis efficiency of derivatives **171n-q** improved to 40-60%.

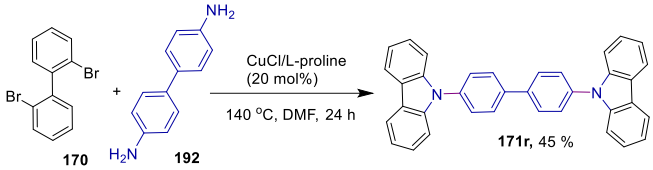
The structures of carbazole compounds **171a-q** were confirmed by spectroscopic methods such as ^{1}H NMR, ^{13}C NMR. Figures 13 and 14 show the ^{1}H NMR and ^{13}C NMR spectra of compound **171a**.

In the ^{1}H-NMR spectrum of compound **171e**, signals corresponding to all 14 protons present in the molecule are observed. A singlet signal of high intensity

at a chemical shift of 5.49 ppm is characteristic of the methylene proton in the benzyl ring. A doublet-triplet signal at 7.34 ppm is attributed to the two protons H-2' and H-6', while another doublet-triplet signal at 7.11 ppm corresponds to the protons H-3' and H-5' in the benzyl ring. Signals from the remaining 8 aromatic protons are observed in the range of 8.13-6.94 ppm.

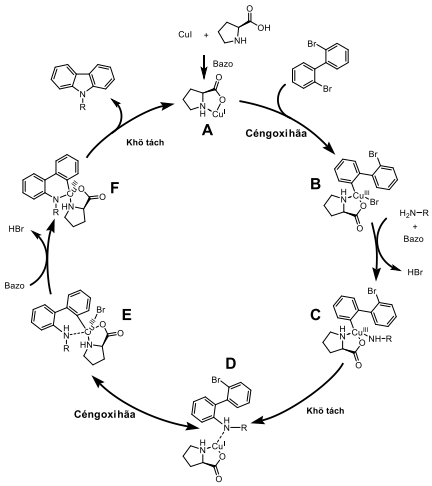
In the ^{13}C NMR spectrum of compound **171e**, signals from all 19 carbon atoms present in the molecule are observed. The carbon atom C4' directly bonded to the fluorine atom exhibits a doublet signal at 162.38 ppm with a coupling constant (*J*) of 245.6 Hz. A doublet signal at 128.27 ppm with J = 8.1 Hz is characteristic of C-2' and C-6', while a doublet signal at 115.90 ppm with J = 21.8 Hz corresponds to C-3' and C-5'. The carbon atoms CH_2 in the benzyl ring resonate at 46.17 ppm.

Additionally, under optimized conditions, the research group successfully synthesized bis-carbazole compound **171r** (a commercial material for OLED fabrication) *via* the reaction between 2,2'-dibromodiphenyl and diamine 192 with a yield of 45% (Scheme 56).



*Scheme 56. Synthesis of bis-carbazole compound **171r***

The proposed mechanism for the synthesis of 9*H*-carbazole compound is described in Scheme 57. Initially, the oxidative addition of Cu(I) catalyst with L-proline forms Cu(I) complex (A). Intermediate complex A participates in oxidative addition reaction with 2,2'-dibromodiphenyl (**170**) to form Cu(III) intermediate complex (B). Intermediate complex B further reacts with quaternary ammonium salt (obtained in situ from the reaction between amine and base) to generate intermediate complex C. Subsequently, intramolecular oxidative addition processes occur, leading to carbazole product formation and regeneration of complex A for the next reaction cycle.

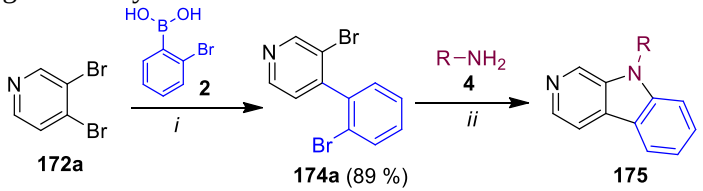


Scheme 57. Proposed mechanism for the synthesis of 9H-carbazole compound ***171***

3.3. Synthesis of δ-carboline and β-carboline derivatives

3.3.1. Synthesis of β-carboline using Pd catalyst

There are various methods for synthesizing carboline compounds, among which transition metal-catalyzed cyclization reactions are of particular interest due to their advantages such as selective reactivity and high efficiency. Starting from the substrate 3,4-dibromopyridine **172a**, we conducted a selective Suzuki-Miyaura reaction with 1.2 equivalents of *o*-bromophenylboronic acid, employing 5 mol% $Pd(PPh_3)_4$ catalyst, to obtain the intermediate product 3-bromo-4-(2-bromophenyl)pyridine **175a** with a yield of 89%. Subsequently, this intermediate product was subjected to coupling reactions with various amine derivatives *via* double C-N bond formation, utilizing Pd catalyst, to yield β-carboline derivatives **5** with high efficiency.

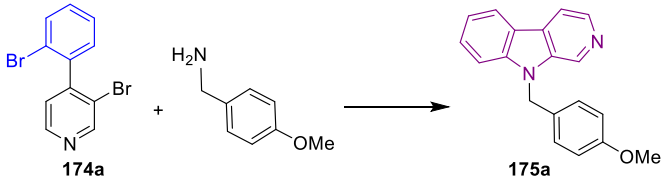


Scheme 58. Synthesis of β-carboline derivatives ***175***

Reaction conditions: i. 173 (1.2 equiv.), $Pd(PPh_3)_4$ (5 mol-%), 1M K_2CO_3 (25 mL), 10% KOH (5 drops), tetrahydrofuran (THF) (35 mL), reflux, 24 h; (ii) 4

(3 equiv.), NaOtBu (6 equiv.), $Pd_2(dba)_3$ (5 mol-%; dba = dibenzylideneacetone), 10% of 1,1-bis(diphenylphosphino)ferrocene (dppf) ligand; toluene, 110 °C, 7 h.

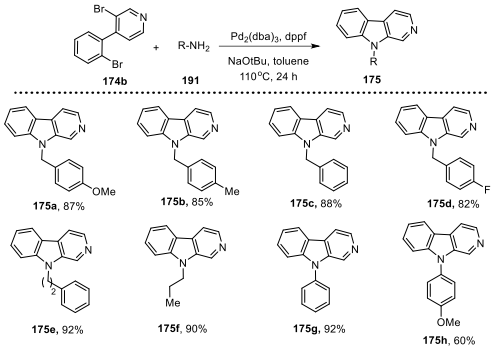
To optimize the reaction, we investigated the cyclization reaction of **174a** with 3,5-dimethoxyaniline **191c**, monitored by ^{1}H NMR spectroscopy using 1,4-dioxane as an internal standard. Several key factors affecting the reaction were explored, including the source of Pd, ligands, solvents, and reaction temperature. The results showed that monodentate ligands such as Xphos, SPhos, $PCy_3{\cdot}HBF_4$, $P(t\text{-}Bu)_3{\cdot}HBF_4$ yielded moderate reaction efficiency (entries 6-11). In contrast, bidentate ligands showed better efficiency, particularly when using a combination of Pd_2dba_3 with Dppf, resulting in a yield of up to 97%. Substituting Pd source with $Pd(OAc)_2$ led to lower efficiency (55%). Examination of organic solvents revealed that toluene was the most suitable solvent for the reaction. Therefore, the optimized conditions for this reaction are $Pd_2(dba)_3$ catalyst, Dppf ligand, NaOtBu base, toluene solvent, and 110°C temperature.



*Scheme 59. Synthesis of β-carboline derivatives **175a***

*Table 1. Optimization of the synthesis reaction of β-carboline derivatives **175a***

Entry	Catalyst	Ligand	Base	Solvent	Yield (%)[a]
1	$Pd(OAc)_2$	BINAP	NaO*t*Bu	Toluene	47
2	$Pd_2(dba)_3$	BINAP	NaO*t*Bu	Toluene	72
3	$Pd_2(dba)_3$	XantPhos	NaO*t*Bu	Toluene	83
4	$Pd_2(dba)_3$	DpePhos	NaO*t*Bu	Toluene	80
5	**$Pd_2(dba)_3$**	**Dppf**	**NaO*t*Bu**	**Toluene**	**87**
6	$Pd_2(dba)_3$	dppe	NaO*t*Bu	Toluene	25
7	$Pd_2(dba)_3$	XantPhos	KO*t*Bu	Toluene	41
8	$Pd_2(dba)_3$	XantPhos	$CsCO_3$	Toluene	27
9	$Pd_2(dba)_3$	XantPhos	NaO*t*Bu	DMSO	13
10	$Pd_2(dba)_3$	XantPhos	NaO*t*Bu	1,4-dioxane	52
11	$Pd_2(dba)_3$	XantPhos	NaO*t*Bu	DMF	38

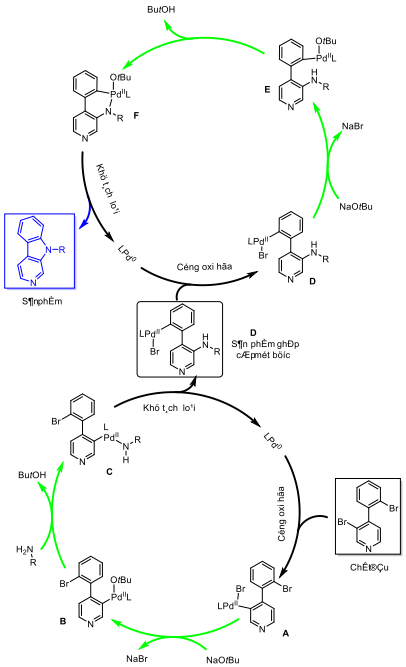


*Scheme 60. Synthesis of β-carboline compounds **175***

In the ^{1}H-NMR spectrum of compound **175c**, a singlet signal appears at 8.86 ppm, attributed to the proton H-1. A singlet signal of high intensity at 5.52 ppm is characteristic of the methylene proton in the benzyl ring. The methoxy - OCH_3 protons resonate as singlets at 3.74 ppm. The remaining protons resonate in the range of 8.47 – 6.77 ppm. In the ^{13}C NMR spectrum of compound **175a**, signals from all 19 carbon atoms present in the molecule are observed.

Applying the optimized conditions, we conducted cyclization reactions between compound **174b** and various aniline derivatives, achieving good yields ranging from 62-95% (**177a-j**). For electron-withdrawing substituents, lower yields were observed compared to electron-donating substituents. The cyclization reaction between compound **174b** and chain amines under these conditions also yielded good results. The structures of derivatives **175a-o** were determined by NMR spectroscopy.

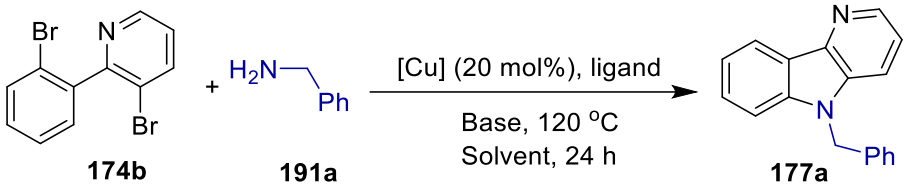
The proposed reaction mechanism is illustrated in Scheme 61. Starting material 3-bromo-4-(2-bromophenyl)pyridine undergoes oxidative addition reaction with LPd(0) to form intermediate Pd(II) complex (A). Intermediate complex A undergoes ligand exchange reaction with NaOtBu base to generate intermediate complex B. Intermediate complex B reacts with amine to yield intermediate complex C. The reductive elimination reaction of intermediate C forms intermediate D, the product of the first coupling reaction, and regenerates the initial Pd(0) catalyst for the next Pd catalytic cycle. Intermediate D continues to undergo ligand exchange reaction with NaOtBu base to form intermediate complex E. Intermediate complex E reacts with amine to yield intermediate complex F. The reductive elimination reaction of intermediate F produces intermediate D, the β-carboline product, and regenerates the initial Pd(0) catalyst.



Scheme 61. Mechanism of the synthesis reaction of β-carboline derivatives

3.3.2. Synthesis of β-carboline and δ-carboline using Cu catalyst

In this thesis, we successfully synthesized several carboline rings through double C-N coupling reactions using the Pd catalyst as described above. However, this method has some limitations such as the expensive Pd catalyst and narrow reaction scope. The application of inexpensive, stable, and readily available copper salts instead of costly transition metal catalysts combined with expensive ligands is of considerable interest in organic synthesis nowadays. We investigated the synthesis of carbazole derivatives using Cu catalysts [18]. To explore further applications in C-N coupling reactions with the presence of Cu catalysts, we conducted research on the synthesis of β- and δ-carboline derivatives from readily available starting materials using copper salt catalysts with the aim of providing a new synthesis method with high productivity, high selectivity, and expanded reaction scope. The optimal conditions for the synthesis of δ-carboline derivatives **177** are described in Table 4.



*Scheme 62. Synthesis of δ-carboline derivatives **177a***

*Table 4. Optimization of the synthesis reaction of δ-carboline derivatives **177a***

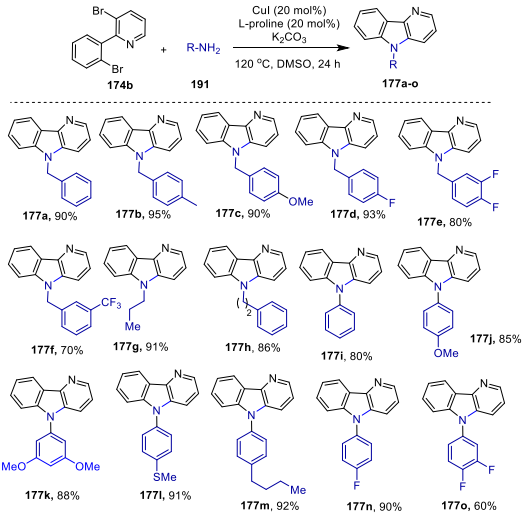
Entry	Catalyst	Ligand	Base	Solvent	Yield (%)a
1	CuI	BINAP	K_2CO_3	DMSO	45
2	CuI	dppe	K_2CO_3	DMSO	36
3	CuI	IPr.HCl	K_2CO_3	DMSO	52
4	CuI	1,10-phenanthroline	K_2CO_3	DMSO	42
5	CuI	bipyridine	K_2CO_3	DMSO	40
6	**CuI**	**L-proline**	**K_2CO_3**	**DMSO**	**90**
7	CuI	L-proline	K_3PO_4	DMSO	79
8	CuI	L-proline	Cs_2CO_3	DMSO	82
9	CuI	L-proline	KO*t*Bu	DMSO	47
10	CuI	L-proline	KOH	DMSO	72
11	CuBr	L-proline	K_2CO_3	DMSO	85
12	CuCl	L-proline	K_2CO_3	DMSO	83
13	CuI	L-proline	K_2CO_3	DMF	82
14	CuI	L-proline	K_2CO_3	NMP	85
15	CuI	L-proline	K_2CO_3	Dioxane	-
16	-	L-proline	K_2CO_3	DMSO	-

[a] The obtained yields were determined by column chromatography purification method.
174b (1.3 mmol), **191a** (2.0 equiv.), base (3 equiv.), [Cu] catalyst (20 mol%), ligand (20 mol%), 120 °C, 24 h.

The double C-N coupling reaction between compound **174b** (1.3 equivalents) and benzylamine **191a** (2.0 equivalents) was conducted to investigate the optimal reaction conditions. Initially, the reaction was performed at 120°C for 24 hours in the presence of CuI catalyst (20 mol%), K_2CO_3 base, and DMSO solvent. Several ligands such as BINAP, dppe, Ipr, 1,10-phenanthroline, and

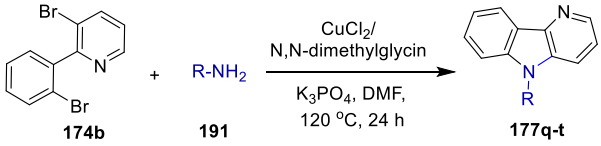
bipyridine were tested, however, they all resulted in low synthesis yields of carboline **177a** ranging from 36-52% (entries 1-5, Table 1). L-proline was found to be the most suitable ligand for this reaction, achieving a synthesis yield of 90% for compound **177a** (entry 6). When substituting K_2CO_3 with other bases such as K_3PO_4, KOH, KOtBu, Cs_2CO_3 (entries 7-10), K_2CO_3 remained the most suitable base. Substituting CuI with other common copper salts such as CuBr, CuCl (entries 11-12) resulted in synthesis yields of compound **177a** of approximately 83-85%, lower than when using CuI catalyst. Next, the influence of several solvents (DMSO, NMP, DMF, dioxane) on the yield was investigated (entries 13-15). The results showed that DMSO was the most suitable solvent for the synthesis reaction of compound **177a** (entry 6). Additionally, when the catalyst was not used, no reaction occurred (entry 16). Therefore, the optimal reaction conditions for the synthesis of δ-carboline compound **177a** are as follows: CuI catalyst (20 mol%), K_2CO_3 base, *L*-proline ligand (20 mol%), 120°C, 24 hours.

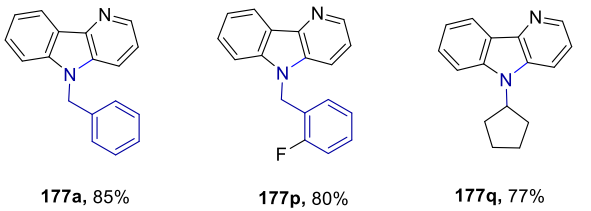
The structure of compound **177a** was determined using nuclear magnetic resonance spectroscopy methods. In the ^{1}H-NMR spectrum of compound **177a**, a singlet signal of high intensity appears at 5.45 ppm, characteristic of the methylene proton in the benzyl ring. A doublet-doublet signal at 8.55 ppm is attributed to the proton H-2. The remaining protons resonate in the range of 8.43-7.06 ppm. In the ^{13}C NMR spectrum of compound **177a**, signals from all 18 carbon atoms present in the molecule are observed. The CH_2 carbon atom in the benzyl ring resonates at 46.56 ppm.



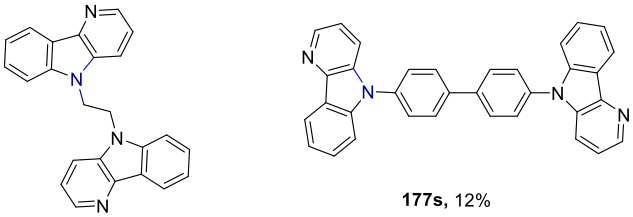
*Scheme 63. Synthesis of δ-carboline derivatives **177a-o** using CuI catalyst*

Applying the optimized reaction conditions as described above, 15 δ-carboline derivatives **177a-o** were synthesized with yields ranging from 60-95% (Table 2). Generally, the reaction between compound **174a** and electron-donating substituent-containing amines (methyl, methoxy) showed higher reaction efficiency compared to amines containing electron-withdrawing substituents. The structures of the δ-carboline compounds **177a-o** were confirmed using modern spectroscopic methods such as ^{1}H NMR, ^{13}C NMR.





177a, 85% **177p,** 80% **177q,** 77%

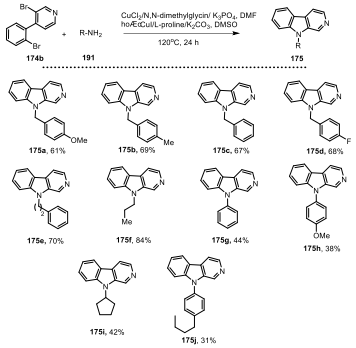


177r, 15% **177s,** 12%

*Scheme 64. Synthesis of δ-carboline derivatives **177q-t** using $CuCl_2$ catalyst*

When using $CuCl_2$ catalyst, *N,N*-dimethylglycine, K_3PO_4, and DMF solvent, we synthesized an additional 4 δ-carboline compounds **177p-s** from various amines according to Scheme 64.

Similarly, using CuI and $CuCl_2$ catalysts, 10 β-carboline derivatives **175a-h** were successfully synthesized through cyclization reactions between compound **174b** and amines **191a-h**. The synthesis yields of the β-carboline compounds **175a-h** ranged from 31-84% (Scheme 65)



*Scheme 65. Synthesis of β-carboline compounds **175** using Cu catalyst*

Experimental results showed that the synthesis yields of β-carboline compounds **175** were lower when using CuI catalyst compared to using Pd catalyst. However, CuI catalyst is more cost-effective and has a wider reaction scope.

*Table 3. Comparison of synthesis yields of β-carboline derivatives **175***

Entry	Product	R	Yield (%)[a]	Yield (%)[b]
1	**175a**	4-MeO-C_6H_4-CH_2-	87	61
2	**175b**	4-Me-C_6H_4-CH_2-	85	69
3	**175c**	Ph	88	67
4	**175d**	4-F-C_6H_4-CH_2-	82	68
5	**175e**	$PhCH_2CH_2$-	92	70
6	**175f**	$CH_3CH_2CH_2$-	90	84
7	**175g**	C_6H_5-	92	44
8	**175h**	4-MeO-C_6H_4-	60	38
[a] $Pd_2(dba)_3$, Dppf, NaOtBu, toluene, 110°C [b] CuI, *L*-proline, K_2CO_3, DMSO, 120 °C				

CONCLUSION

With the aim of investigating new catalysts and optimal conditions for C-N coupling reactions to synthesize diverse heterocyclic compounds, the thesis has achieved the following results:

1. A suitable catalyst system consisting of $Pd_2(dba)_3$/CuI (5 mol% / 10 mol%), XantPhos ligand (10 mol%), NaOtBu base, and toluene solvent at 110°C for approximately 12 hours was developed to synthesize 09 derivatives of 5-aryl-5*H*-pyrido[2',1':2,3]imidazo[4,5-*b*]indole (PIDI) **167a-**

i through C-N coupling reactions. The synthesis yields ranged from approximately 61-76%.

2. A suitable catalyst system consisting of $Pd_2(dba)_3$/CuI (5 mol% / 10 mol%), XantPhos ligand (10 mol%), NaOtBu base, and toluene solvent at 110°C for approximately 12 hours was developed to synthesize 06 derivatives of 8-methyl-5-aryl-5*H*-pyrido[2',1':2,3]imidazo[4,5-*b*]indole **169a-f** through C-N coupling reactions between 2-(2-bromophenyl)-3-iodo-6-methylimidazo[1,2-a]pyridine and various amines. The synthesis yields ranged from approximately 52-83%.

3. A suitable catalyst system consisting of CuCl and CuI with the presence of *L*-proline ligand and base was developed to synthesize 17 carbazole derivatives **171a-r** through two-step *N*-aryl hation reactions between 2,2'-dibromodiphenyl and primary amines, and 17 δ-carboline derivatives **177a-s** through reactions between 3-bromo-2-(2-bromophenyl)pyridine and primary amines. The synthesis yields ranged from approximately 40-95%.

4. A suitable catalyst system consisting of $Pd_2(dba)_3$ and Dppf ligand was developed to synthesize 10 β-carboline derivatives **175a-j** through C-N coupling reactions between 3-bromo-4-(2-bromophenyl)pyridine and primary amines. The synthesis yields ranged from approximately 62-95%.

THE NOVEL CONTRIBUTIONS OF THE THESIS

1. For the first time, the study has developed CuCl and CuI in conjunction with *L*-proline as catalysts for the double C-N coupling reaction to synthesize carbazole derivatives from 2,2'-dibromobiphenyl and amines. This method can be applied to various functional groups, reacting with both aromatic and aliphatic amines, without the need for rare metal catalysts.

2. Initially employing Cu catalysts along with *L*-proline for the C–N coupling reaction to synthesize β- and δ-carboline from dibromopyridine and amines. This method is applicable to diverse functional groups, reacting with both aromatic and aliphatic amines, achieving high yields and selectivity.

3. Pioneering the development of a synthetic method for organic PIDI compounds, with potential applications in pharmaceuticals and materials. This approach relies on a domino process involving two C–N coupling reactions utilizing Pd and Cu catalysts, eliminating the use of toxic isocyanide compounds as previously reported. The method enables the synthesis of multiple PIDI derivatives with high yields (61–76%). The

structures of the synthesized compounds were confirmed using MS, NMR spectroscopy, and single-crystal X-ray diffraction methods.

THE THESIS'S RELATED PAPERS

1. Trần Quang Hưng, Nguyen Minh Quan, Hoang Van Dong, Trinh Duy Nguyen, Hoang Le Tuan Anh, Trieu Quy Hung, Nguyen Van Tuyen, Ngo Thi Thuan, Tuan Thanh Dang, Peter Langer. Synthesis of 5-aryl-5H-pyrido[2',1':2,3]imidazo[4,5-b]indoles by domino Pd- and Cu-catalyzed C–N coupling reactions. Synlett 2019, 30, 3, 303-306.

2. Trần Quang Hưng, Nguyễn Minh Quân, Bàn Văn Phúc, Nguyễn Quyết Tiến, Nguyễn Ngọc Tuấn, Nguyễn Quảng An, Trương Thị Thanh Nga, Nguyễn Ngọc Thanh, Đặng Thanh Tuấn. Phát triển hệ xúc tác lưỡng kim loại (Pd và Cu) đồng thể trong tổng hợp hệ dị vòng 8-methyl-5-aryl-5H-pyrido[2',1':2,3]imidazo[4,5-b]indole. Tạp chí xúc tác và hấp phụ Việt Nam, 2019, 8, 1, 76-81.

3. Ha Nam Do, Nguyen Minh Quan, Ban Van Phuc, Dinh Van Tinh, Nguyen Tien Quyet, Truong Thi Thanh Nga, Van Tuyen Nguyen, Tran Quang Hung, Tuan Thanh Dang, Peter Langer. Efficient copper-catalysed synthesis of carbazoles by double
N-arylation of primary amines with 2,2′-dibromobiphenyl in the presence of air. Synlett 2021, 32, 611-615.

4. Ban Van Phuc, Ha Nam Do, Nguyen Minh Quan, Nguyen Ngoc Tuan, Nguyen Quang An, Nguyen Van Tuyen, Hoang Le Tuan Anh, Tran Quang Hung, Tuan Thanh Dang, Peter Langer. Copper-catalyzed synthesis of β- and δ-carbolines by double N-arylation of primary amines. Synlett 2021, 32, 10, 1004-1008.

5. Bàn Văn Phúc, Nguyễn Minh Quân, Nguyễn Hiển, Nguyễn Quyết Tiến, Trương Thị Thanh Nga, Nguyễn Ngọc Tuấn, Nguyễn Quảng An, Cù Hồng Hạnh, Đặng Thanh Tuấn, Trần Quang Hưng. Nghiên cứu phương pháp tổng hợp hiệu quả β- và δ-carboline sử dụng xúc tác đồng. Tạp chí xúc tác và hấp phụ Việt Nam, 2022, 11, 4, 50-56.