Maria Margarida Penhasco Martins

Licenciada em Química

Investigation of the reactivity of aminopyridines on C-H activation reaction: a direct route to azaindoles

Dissertação para obtenção do Grau de Mestre em
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Orientador: Doutora Maria Manuel B. Marques, Professora auxiliar com Agregação, FCT-UNL

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Resumo

Os azaindoles são compostos heterocíclicos aromáticos que apresentam atividade biológica relevante. Contudo, o núcleo de azaindole é particularmente difícil de sintetizar, sendo que a maioria dos métodos reportados requer uma pré-funcionalização dos substratos. A reação de ativação/funcionalização de ligações C–H é um tema emergente que leva os investigadores a considerar estas ligações como um grupo funcional reativo em reações catalisadas por metais. Deste modo, é possível desenvolver aproximações sintéticas que evitem uma pré-funcionalização dos substratos e, consequentemente, mais rápidas e económicas. Contudo, a reação de ativação de ligações C–H ainda está pouco explorada relativamente à síntese de azaindoles, havendo unicamente dois métodos reportados na literatura, restritos para o isómero 7-azaindole.

Neste projeto foi desenvolvido um método para obter o núcleo de azaindole através de uma dupla ativação C–H intramolecular. Para este propósito, foram preparados intermediários extremamente relevantes – iminas/enaminas – através de acoplamento cruzado C–N de aminopiridinas com α-bromoestireno. Assim, através de um procedimento inovador *one-pot* que combina acoplamento cruzado C–N com ativação C–H, foram preparadas seis estruturas distintas de azaindole (I.1–49%, I.2–9%, II.1–37%, III.1–64%, III.2–18%, IV.1–5%), sendo as três primeiras descritas pela primeira vez.

Foram testados e otimizados diferentes sistemas catalíticos para as reações de acoplamento cruzado C–N e ativação C–H para cada aminopiridina, tendo-se verificado que a reatividade das mesmas varia consideravelmente consoante a posição relativa do grupo amina bem como o padrão de substituição no anel de piridina.

Para o acoplamento cruzado C–N, foram utilizados os sistemas Pd_2dba_3/**XPhos**/*t*-BuONa (I.1/I.2, III.1/III.2 e IV.1) e Pd_2dba_3/**XantPhos**/*t*-BuONa (II.1), enquanto que para a ativação C–H foram testados $Pd(OAc)_2$/**$Cu(OAc)_2$**/**Cs_2CO_3** (I.1/I.2) e $Pd(OAc)_2$/**Ag_2CO_3**/**PivOH** (II.1, III.1/III.2 e IV.1). Durante o processo de otimização da ativação C–H, verificou-se que a adição de sais de prata tinha uma forte influência na regiosseletividade da reação. A maior conversão observada foi de 82% para o azaindole não substituído III.1/III.2.

Adicionalmente, foi testada como uma alternativa para obter a imina/enamina, uma reacção de condensação de cetonas com aminopiridinas. Contudo verificou-se que a condensação não era eficiente nas condições aplicadas e este método podia potencialmente beneficiar de um procedimento passo-a-passo, ao invés de *one-pot*.

Por último, investigou-se o mecanismo reacional, bem como o equilíbrio imina/enamina, com base em dados de NMR e computacionais.

Palavras-chave: azaindole; reações catalisadas por paládio; acoplamento cruzado C–N; ativação/funcionalização C–H; reações CDC; regiosseletividade.

Abstract

Azaindoles are relevant heterocyclic aromatic organic compounds that exhibit interesting biological activity. However, the azaindole core is challenging to achieved and most reported methods require the pre-functionalization of substrates. The C–H activation/functionalization reaction is an emergent topic, as organic scientists look at C–H bonds as reactive functional groups in metal-catalyzed reactions, avoiding the pre-functionalization of substrates and resulting in an approach that is less time and cost consuming plus environmentally friendly. C–H activation reactions are scarce regarding azaindole synthesis and, up to date, only two examples can be found in the literature which are restricted to the 7-azaindole isomer.

In this project, a methodology to attain the azaindole core through dual intramolecular C–H activation has been developed. For this purpose, very important synthetic intermediates – imines/enamines – have been prepared from C–N cross-coupling reaction of aminopyridines and *α*-bromostryrene. In an one-pot procedure, this unique C–N cross-coupling/C–H activation reaction allowed to obtain six azaindole structures (I.1–49%, I.2–9%, II.1–37%, III.1–64%, III.2–18%, IV.1–5%), with the first three reported for the first time.

Different catalytic systems for C–N cross-coupling and C–H activation reactions have been tested and manipulated in order to obtain the best conditions for each aminopyridine. A different reactivity was observed for each aminopyridine, depending on the presence of substituents and the substitution pattern in the pyridine ring.

For the C–N cross-coupling reaction, Pd_2dba_3/**XPhos**/*t*-BuONa (I.1/I.2, III.1/III.2 and IV.1) and Pd_2dba_3/**XantPhos**/*t*-BuONa (II.1) were applied and for the C–H activation reaction $Pd(OAc)_2$/**$Cu(OAc)_2$**/**Cs_2CO_3** (I.1/I.2) and $Pd(OAc)_2$/**Ag_2CO_3**/**PivOH** (II.1, III.1/III.2 and IV.1). The best yield obtained was for unsubstituted azaindole III.1/III.2, with a total conversion of 82%. Additionally, the addition of silver salts on the C–H activation reaction demonstrated to influence the regioselectivity.

Ketone condensation with aminopyridines was tested as an alternative method to obtain the imine/enamine. It was concluded that the condensation reaction wasn't efficient under the tested reaction conditions and better results might be obtained via a stepwise ketone condensation/C–H activation procedure.

Finally, a mechanistic proposal was undertaken based on NMR data, computational calculations and literature.

Keywords: azaindole; palladium catalyzed reactions; C–N cross-coupling; C–H activation/functionalization; CDC reactions; regioselectivity.

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Abbreviations and Symbols

Ac – Acetyl

ACN – Acetonitrile

Ar – Aryl

ATP – Adenosine Triphosphate

ATR – Attenuated Total Reflection

BINAP – (2,2′-bis(diphenylphosphino)-1,1′-binaphthyl)

CDK – Cyclin-Dependant Kinases

cBRIDP – Di-tert-butyl(2,2-diphenyl-1-methyl-1-cyclopropyl)phosphine

c-Met – Receptor tyrosine kinase

Cy – Cyclohexyl

dba – Dibenzylideneacetone

DCE – 1,2-Dichloroethane

DFT – Density Functional Theory

DMF – Dimethylformamide

DMSO – Dimethylsulfoxide

dppe – 1,2-bis(diphenylphosphanyl)ethane

dppf – 1,1'-Bis(difenilfosfino)ferrocen

equiv. – Equivalents

FDA – Food and Drug Administration

FTIR – Fourier-Transform Infrared Spectroscopy

GSK-3β – Glycogen synthase kinase 3 beta

GFP – Green Fluorescent Proteins

h – hours

HIV – Human Immunodeficiency Virus

HPMV – High Pressure Mercury Vapor

***i*-Pr** – Isopropyl

MCCCRs – Metal-catalyzed cross-coupling reactions

MS – Mass spectrometry

MW – Microwave

NMR – Nuclear Magnetic Resonance spectroscopy

RT – Room temperature

TBAB – Tetrabutylammonium bromide

***t*-Bu** – *tert*-butyl

TLC – Thin-layer chromatography

Tf – Triflate

TPGS-750-M – DL-*α*-Tocopherol methoxypolyethylene glycol succinate solution

p38 MAP – Mitogen-activated Protein

Piv – pivaloyl

Ph – Phenyl

XantPhos – 4,5-Bis(diphenylphosphino)-9,9-dimethylxanthene

XPhos – 2-Dicyclohexylphosphino-2′,4′,6′-triisopropylbiphenyl

NMR assignment terms:

s – Singlet

d – Doublet

t – Triplet

m – Multiplet

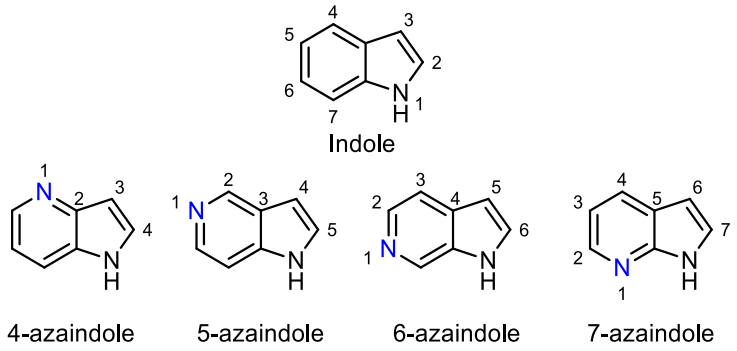
δ – Chemical shift

Chapter 1 - Introduction

1.1. The azaindole nucleus

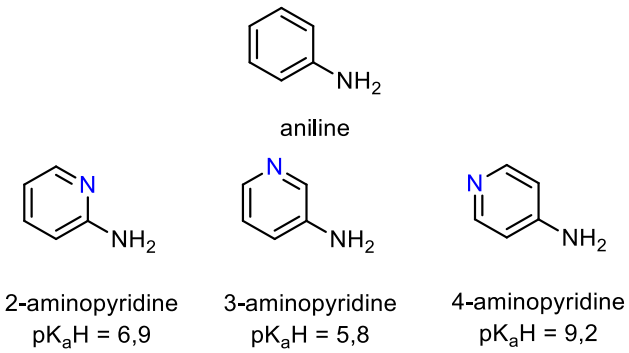
1.1.1. Azaindole, indole and aminopyridines

Azaindoles are heterocyclic aromatic organic compounds that have a bicyclic structure, consisting of a pyrrole ring fused to a pyridine ring. They are bioisosteres of the indole nucleus, meaning they can produce similar biological activity, due to its similarity in chemical and physical properties. Since the indole is an extremely important nucleus in medicinal chemistry, being a target molecule in synthesis and biological investigation, the azaindole nucleus has also interest in these areas.[1] Replacement of a carbon by a nitrogen atom at positions 4 to 7 of the indole nucleus, originates the four possible regioisomers of the azaindole nucleus (Scheme 1).



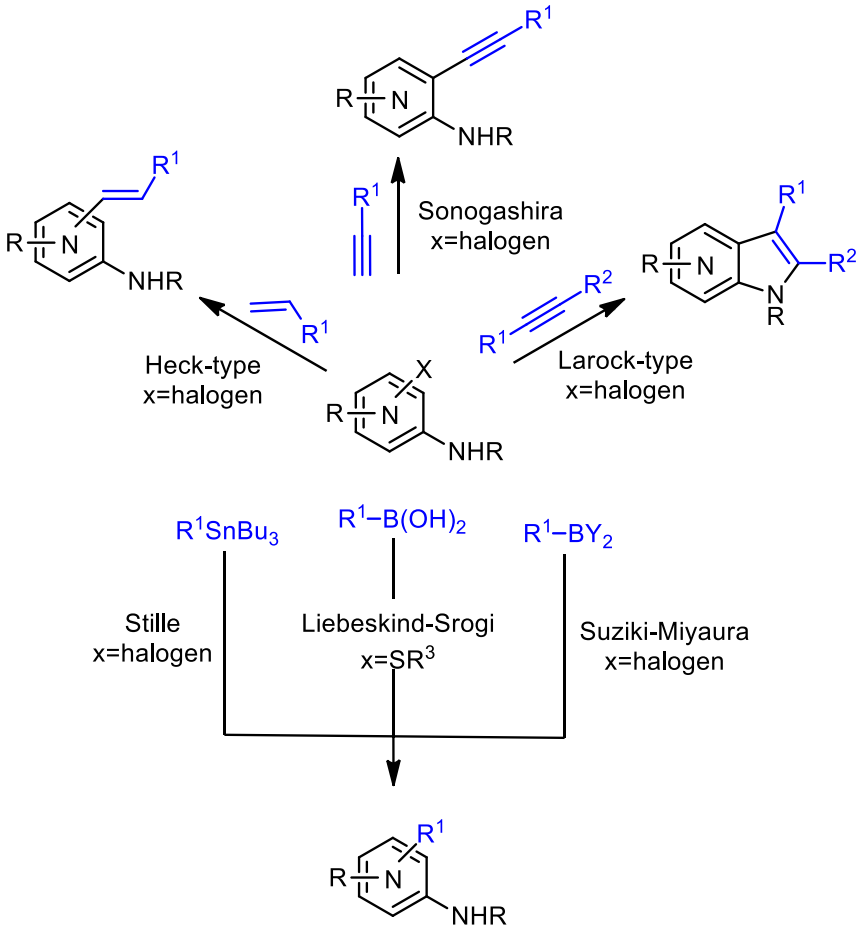
Scheme 1 – Indole nucleus and regioisomers of azaindole nucleus.

Similarly to the indole synthetic methods, that start from anilines, common synthetic methods to prepare azaindole start from the respective aminopyridine, which is why methods of derivatization of aminopyridines are so relevant. However, not only the reactivity of anilines and aminopyridines differs substantially, due to the extra nitrogen atom in the aromatic ring, the position of the nitrogen in the ring also results in very different reactivity between the aminopyridine isomers. [2,3] This can also be immediately observed through the values of pK_aH (Scheme 2).[4]

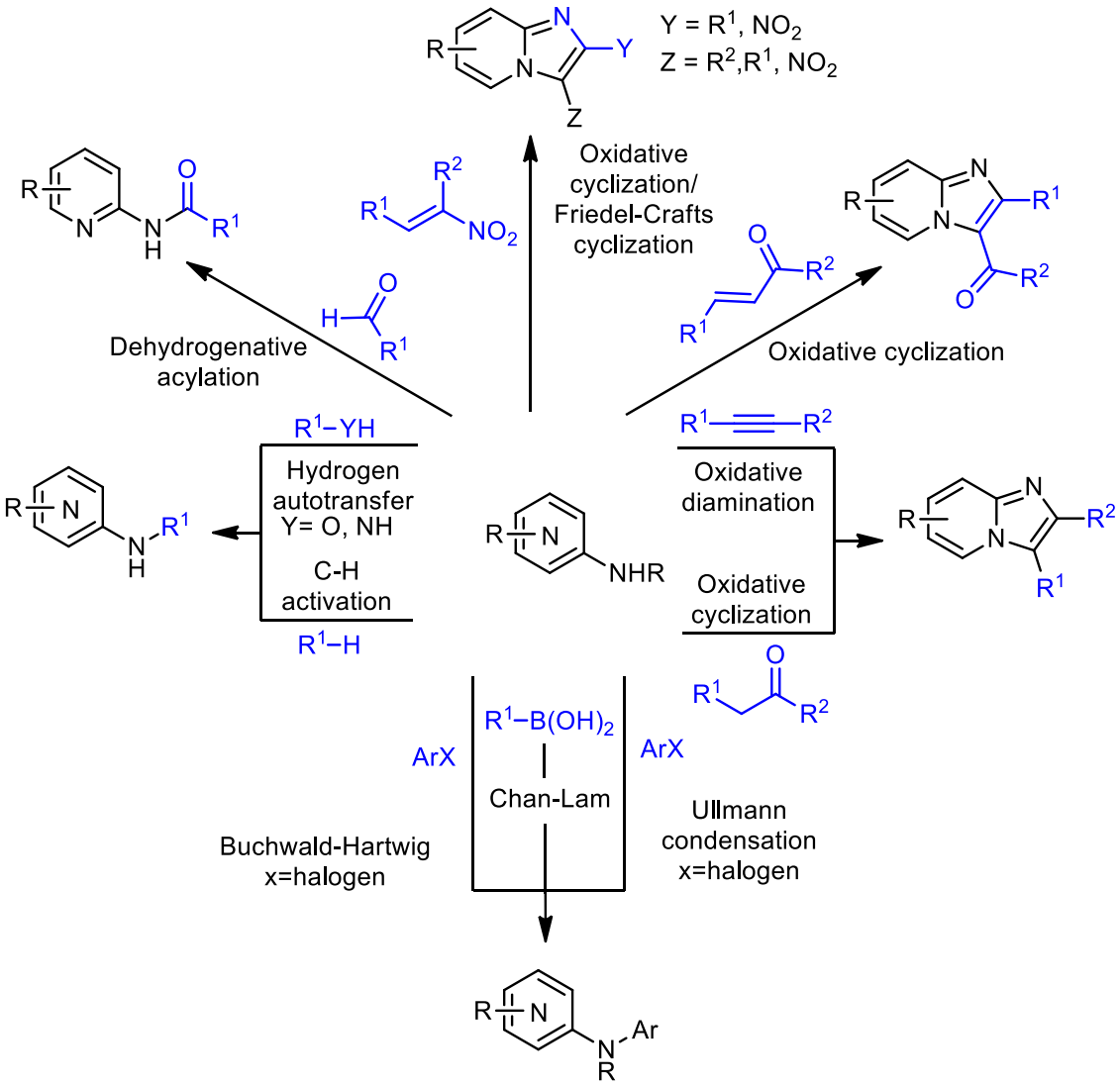


Scheme 2 – Aniline structure and aminopyridine regioisomers with the respective pK_aH values.

Metal-catalyzed cross-coupling reactions (MCCCRs) are highly useful for the construction and derivatization of aminopyridines. However, such reactions with heteroaryl substrates proved to be significantly more challenging than with the all-carbon substrates, as the anilines, since the presence of the nitrogen group in the pyridine ring has been observed to deactivate the catalyst. The most recent synthetic advances in metal-catalyzed methods for both C–C and C–N cross-coupling reactions that allow to obtain different aminopyridine structures are represented in Schemes 3 and 4.



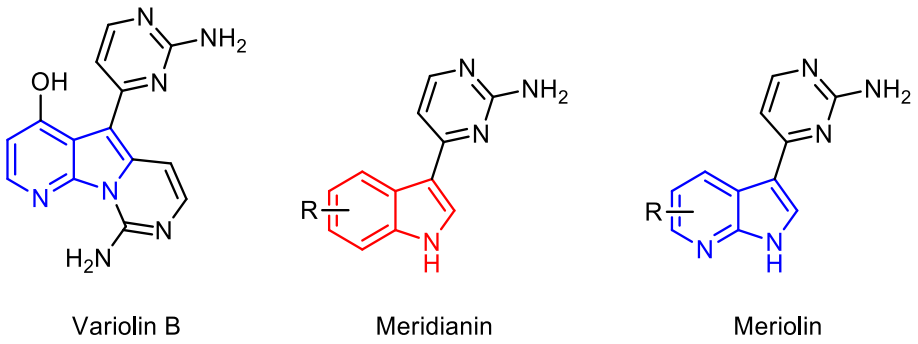
Scheme 3 – Metal-catalyzed C-C coupling reactions of aminopyridines.



Scheme 4 – Metal-catalyzed C–N coupling reactions of aminopyridines.

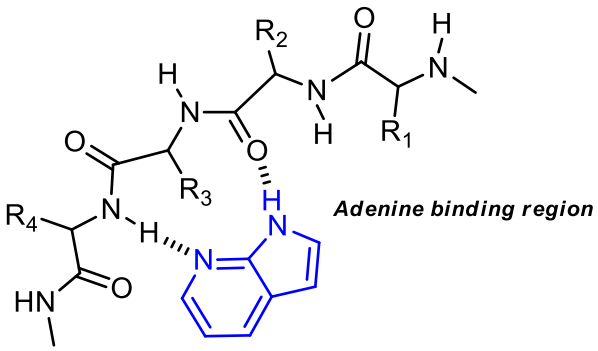
1.1.2. Biological interest and important applications of azaindoles

While the indole nucleus is commonly found in nature, the azaindole core is rare, with only the 7-azaindole isomer existing naturally. This regioisomer was noticed to have significant antitumor activity in the Variolins family, with Variolin B (Scheme 5) being the most active derivative, through inhibition of kinases.[5,6] The presence of an extra nitrogen atom in the nucleus can magnify the biological activity towards kinases when compared to the indole nucleus, since this one can act as an hydrogen bond acceptor, and increase possible fits in the ATP active site (Scheme 6). This was first observed when inhibition of cyclin-dependant kinases (CDK) of Meriadinins was compared to their synthetic analogs – Meriolins – that contain the 7-azaindole nucleus (Scheme 5), and found to further inhibit CDK, plus, also be an antiproliferative and proapoptotic agent.[7,8]



Scheme 5 – Chemical structures containing the azaindole (in blue) and indole (in red) nucleus in Variolin B, Meridianin and Meriolin.

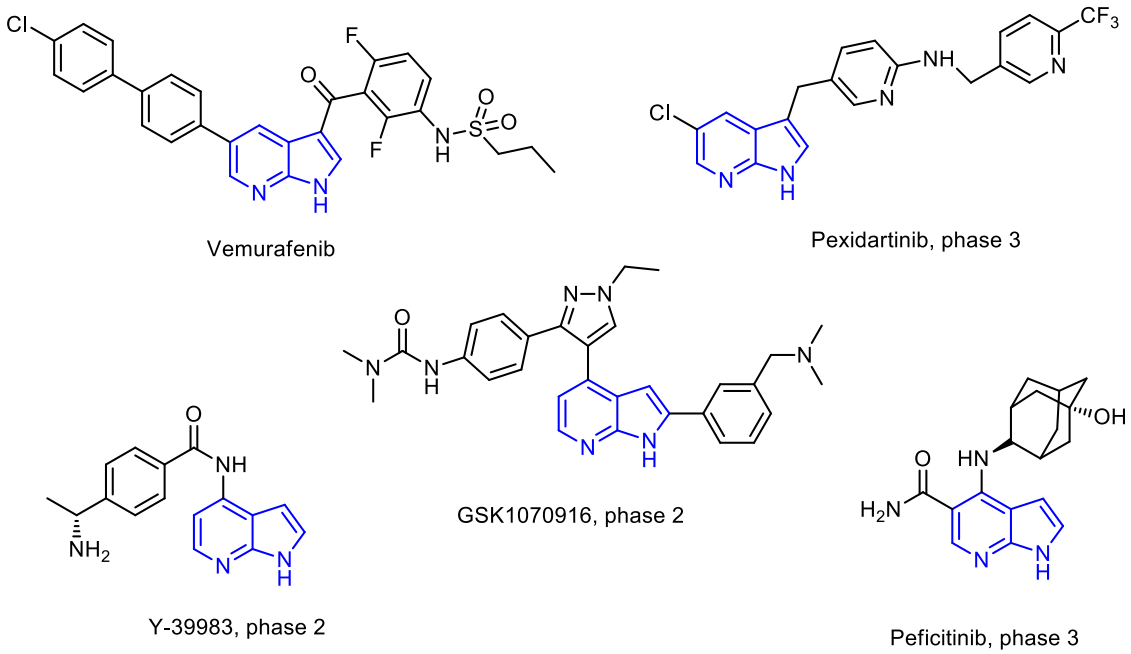
Metal complexes possessing the azaindole nucleus as ligands have also been investigated, with 7-azaindole base ligands showing a very relevant and wide biological activity[9], particularly with a cytotoxicity comparable with the very well-known anticancer drug, *cisplatin*[10].



Scheme 6 – Hydrogen bond acceptor and donor interactions of 7-azaindole in the adenine binding region of ATP active site.

Currently, there is in the market a drug approved by FDA for the treatment of late stage melanoma, Vemurafenib, which contains the 7-azaindole nucleus in its frame. Several other strong candidates are under clinical evaluation (Scheme 7).[11]

Although 7-azaindole has shown to be the most significant isomer for pharmacology due to its simultaneous hydrogen bonding and accepting ability,[11] the other regioisomers are also biologically active, especially in the kinase inhibition area.[6] For example, 4-azaindole has shown to be a very good inhibitor of various kinds of kinase proteins such as GSK-3β (Glycogen synthase kinase 3 beta), c-Met (receptor tyrosine kinase) and p38 MAP (mitogen-activated protein).[12-14] Furthermore, 6-azaindole nucleus was observed to be a greater FLT-3 kinase inhibitor when comparing to the 7-azaindole analog [15] and a 5-azaindole substrate was observed to exhibit HIV reverse transcriptase inhibition.[16]



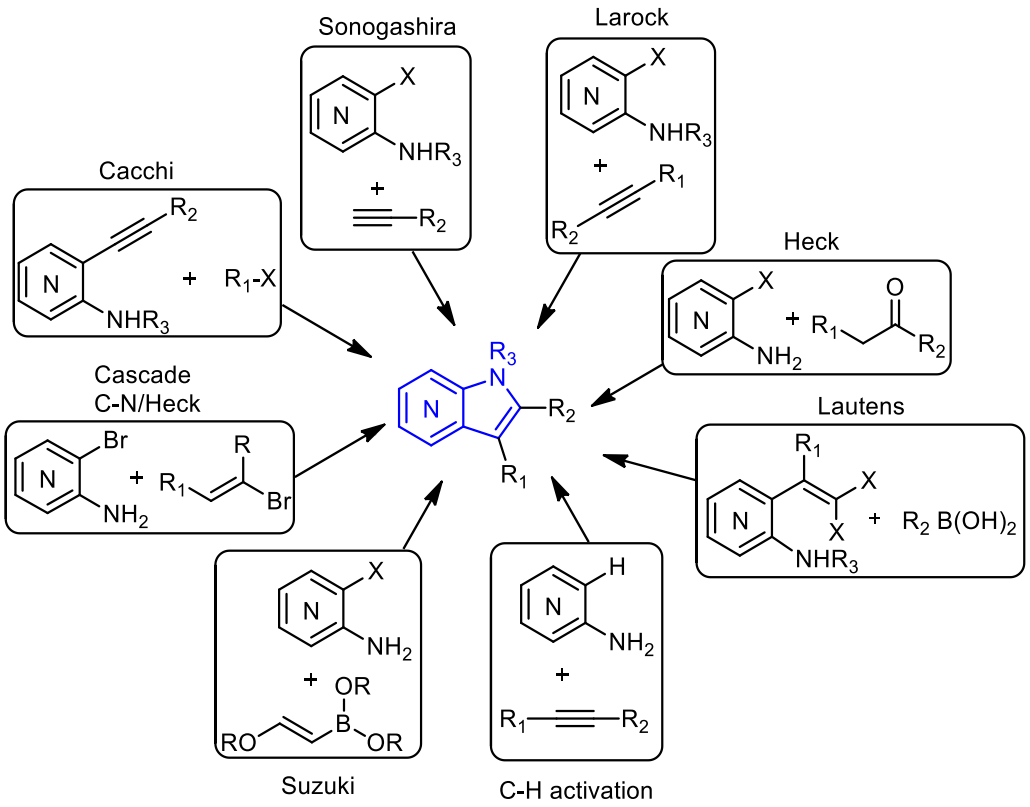
Scheme 7 – Vemurafenib structure and other potential drugs under clinical trials containing the 7-azaindole nucleus.

Besides the pharmacological properties, the azaindole nucleus has also a special place in the material sciences due to its luminescence characteristics. [17] Over the years, the azaindole nucleus has been found in the development of GFP (green fluorescent proteins) for bioimaging[18] and fluorescent chemosensors/probes of fluoride, acetate ions[19] and acidic compounds (detection of H^+).[20]

1.2. Metal-catalyzed methods for azaindole synthesis

Several synthetic methods have been developed for the synthesis of azaindoles, either non-metal-catalyzed or metal-catalyzed. The most relevant ones are almost exclusively metal-catalyzed methods (Scheme 8), since these are the ones that have made a huge impact in the area, providing new, efficient and versatile ways to obtain such challenging compounds.[2,3]

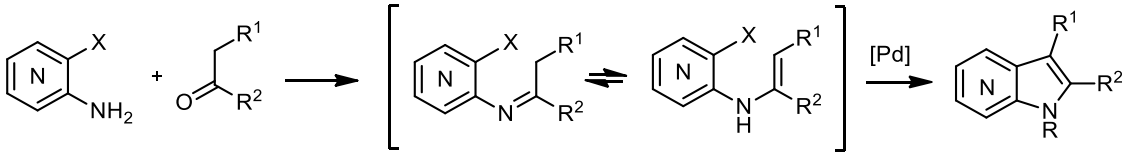
This subchapter focuses on some of the most used metal-catalyzed methods reported up to date for the synthesis of azaindoles.



Scheme 8 – Metal-catalyzed methods in the literature for the synthesis of azaindole.

1.2.1. Heck-type reaction

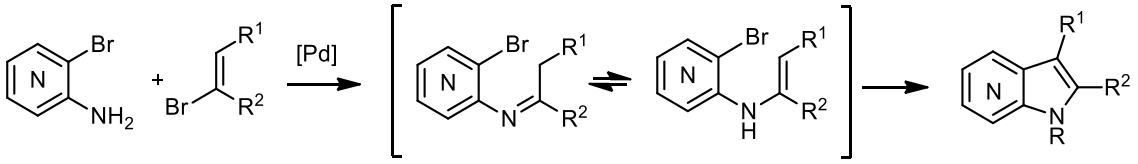
The Heck type reaction is a palladium catalyzed coupling reaction of activated alkenes with aryl halides or vinyl halides. Construction of azaindoles by this method involves direct Pd-catalyzed annulations of *ortho*-halo-substituted aminopyridines with an aldehyde or ketone, involving *in situ* enamine formation, followed by Heck reaction to originate the pyridine ring (Scheme 9) [21, 63]



Scheme 9 – Intramolecular Heck reaction with *in situ* enamine formation for azaindole synthesis.

1.2.2. Cascade C−N cross-coupling/Heck Reaction

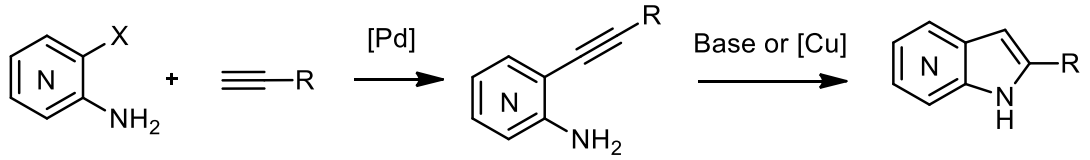
Using the Heck-type reaction, our group has developed an elegant method to synthesize substituted 4-, 5-, 6- and 7-azaindoles (Scheme 10) through a cascade C–N cross-coupling reaction followed by Heck Reaction, in a one-pot manner using only one catalytic system[22]. The Pd(0) complex first catalyzes the C–N cross-coupling to originate an enamine/imine which then immediately suffers intramolecular Heck coupling catalyzed by the re-oxidize palladium complex.



Scheme 10 – Cascade C−N cross-coupling/Heck Reaction in the synthesis of azaindoles.

1.2.3. Sonogashira reaction

The Sonogashira reaction is a C–C cross-coupling type reaction in which aryl or vinyl halides can be coupled with terminal alkynes via palladium catalysis. In the case of azaindole synthesis, the substrate is an *ortho*-halo-substituted aminopyridine that, after Sonogashira reaction with a terminal alkyne, affords an intermediate that suffers cyclization into the azaindole nucleus in the presence of strong bases like potassium hydride or copper-mediated cyclization (Scheme 11).[2-4]

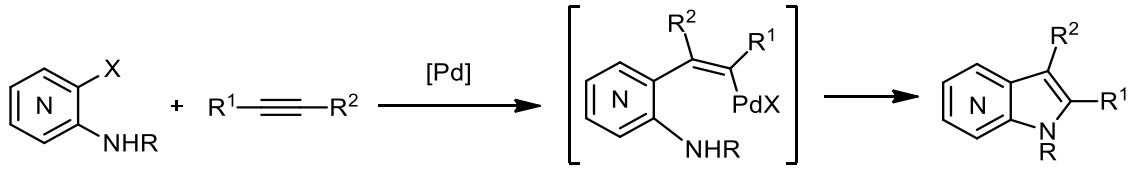


Scheme 11 – Sonogashira type reaction applied in the synthesis of azaindole.

Various authors have reported the use of this reaction in the pursuit of the azaindole moiety[23]. Particularly, our group developed a singular one-pot method that gives access to 1,2-disubstituted 4-, 5-, 6- and 7-azaindoles from amino-*o*-halopyridines, via N-arylation, followed by Sonogashira reaction and final *in situ* cyclization.[24]

1.2.4. Larock reaction

The Larock reaction was primarily reported for the synthesis of the indole nucleus through palladium catalyzed heteroannulation of internal alkenes.[25] After the successful application to the azaindole nucleus, this approach became a common synthetic strategy to obtain all regioisomers properly substituted in the pyridine moiety (Scheme 12).[26] The regioselectivity of the reaction strongly depends on the steric difference between groups R^1 and R^2, and the more sterically demanding group will end up adjacent to the nitrogen in the pyridine ring. Also, the presence of an amino-protecting group R has a major influence in the reaction outcome, since it has been observed that alkyl and aryl groups gave higher yields.[27]



Scheme 12 – Larock type reaction of azaindoles though palladium catalyzed heteroannulation of internal alkenes.

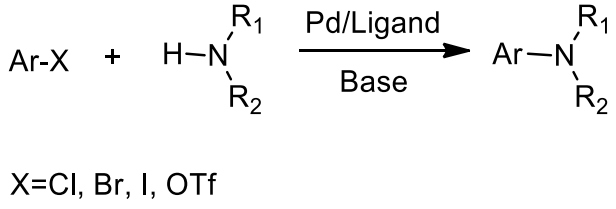
1.3. C–N cross-coupling reactions

1.3.1. The Buchwald-Hartwig amination

As shown in the previous subchapter and chapter, strategies to obtain azaindoles rely mostly in the use of aminopyridine substrates. Because of this, methods for functionalization of aminopyridines that allow the formation of C–N bonds are extremely important, since the resulting intermediates afford different azaindole structures. However, C–N bond formation in this type of substrates constitutes a challenge; as mentioned, the amine group as low nucleophilicity due to the electron-withdrawing nature of the pyridine ring. On top of that, aminopyridines have high affinity to coordinate through the nitrogen in the pyridine ring which causes the poisoning of the metal catalysts.[28]

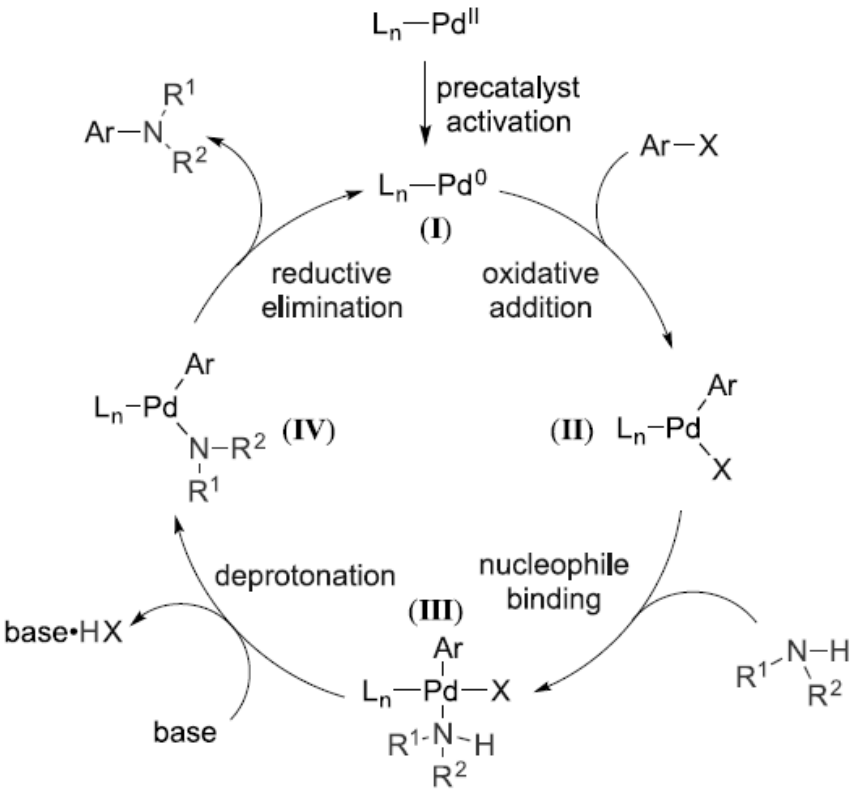
Metal-free methods are generally not practical and require harsh conditions so, the emergence of Pd-catalyzed Buchwald-Hartwig aminations in 1990s,[28,29] had a huge impact on the area and soon extensive research on the formation of C–N bonds inspired by Buchwald-Hartwig work was developed. Even though, originally, the reaction was limited to aryl amines and halides, nowadays it has extended to a variety of substrates and address various reactions and ligands that can be used in secondary amines, primary amines, ammonia, hydrazines, amides, ureas, carbamates, sulfonamides, imidazole and triazoles.[30]

The general representation of the Buchwald-Hartwig amination with palladium-catalyzed C–N cross-coupling is represented in (Scheme 13) and involves coupling of amines (primary or secondary) with aryl (pseudo)halides to afford aryl amines, in the presence of the palladium phosphine-ligand catalyst and a hindered, strong base. [31]



Scheme 13 – General representation of Buchwald-Hartwig amination.

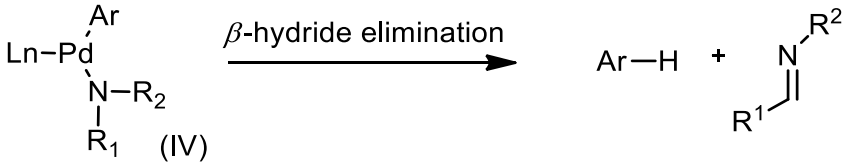
Mechanistic studies of the Buchwald-Hartwig amination have led to the generic mechanism represented in Scheme 14. The catalytic cycle begins with oxidative addition of phosphine-ligated palladium(0) to the aryl (pseudo)halide and originates the palladium(II) complex. Complex **(II)** then acts has a Lewis acid and suffers nucleophilic attack from the amine to form complex **(III)**. Consecutive base-mediated deprotonation eliminates HX to form an amido complex **(IV)** which regenerates the catalyst back to palladium(0) upon reductive elimination and subsequent release of the arylamine product.[30]



Scheme 14 – General catalytic cycle for the Buchwald-Hartwig amination.[30]

A competitive reaction might occur at the reductive elimination step involving a β-hydride elimination of complex **(IV)** (Scheme 15). This prompted investigators to test the use of chelating bidentate phosphine ligands to avoid the arene side product and favor reductive elimination. Studies pointed that the use of catalysts containing electron-rich and modestly hindered chelating phosphines with small bite angles gave the best selectivities for the reductive elimination.[32] However, posterior advances in the development of phosphine ligands, particularly, sterically hindered monophosphine ligands, proved that chelating ligands were not necessarily better to avoid the β -hydride elimination reaction and, in some cases, monodentate ligands were superior.[33]

This initiated the development of the ligands used in the reaction, which, throughout the years, helped to develop a wide range of phosphine ligands that allowed a wider reaction scope, greatly improving the original phosphine ligand, P(*o*-tol)$_3$ (Tri(o-tolyl)phosphine) [31].



Scheme 15 – β-hydride elimination reaction of complex IV to originate an arene product.

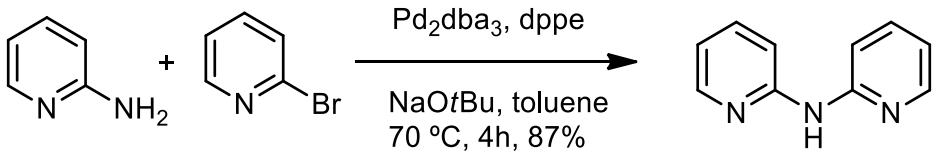
There are various aspects that affect the C–N cross-coupling reaction (palladium source, temperature, solvent, base, among others), but the choice of the phosphine ligand is, undoubtedly, the main factor to consider, since it alters the catalyst structure and reactivity. Depending on the type of amine nucleophile, different ligands are applied.

Palladium sources can be either of palladium(0) (Pd_2dba_3, $Pd(PPh_3)_4$, for example) or palladium(II) ($Pd(OAc)_2$, $PdCl_2$, $[PdCl(allyl)]_2$, for example). In the first case, the catalyst is already in its active oxidation state, but still requires ligand exchange in order to form the catalyst, being, because of this, labeled as a *precatalyst*. Palladium(II) sources must be reduced in order to engage in oxidative addition and, for this purpose, amines, tertiary phosphines, boronic acids, and organometallic reagents have all been reported[34].

1.3.2. Pd-catalyzed C–N cross-coupling reactions of aminopyridines

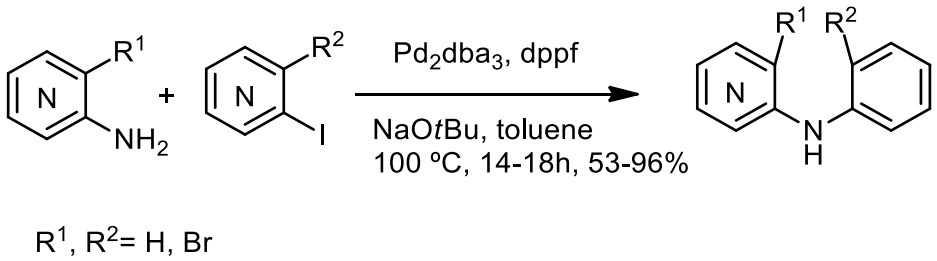
The first palladium-catalyzed C–N cross-coupling reaction of an aminopyridine was reported by Buchwald and Wagaw in 1996.[35] They achieved the diaryl coupling product with 87% yield reacting 2-aminopyridine with 2- bromopyridine in the presence of Pd_2dba_3 catalyst and dppe (1,2-bis(diphenylphosphanyl)ethane) ligand (Scheme 16).

In this case, the use of a chelating ligand proved to be crucial for preventing catalyst poisoning by palladium coordination with the pyridine ring, something the authors primarily noticed when employing the traditional Buchwald-Hartwig amination ligand P(*o*-tolyl)$_3$.



Scheme 16 – First palladium-catalyzed C–N cross-coupling reaction of an aminopyridine reported by Buchwald and Wagaw[35].

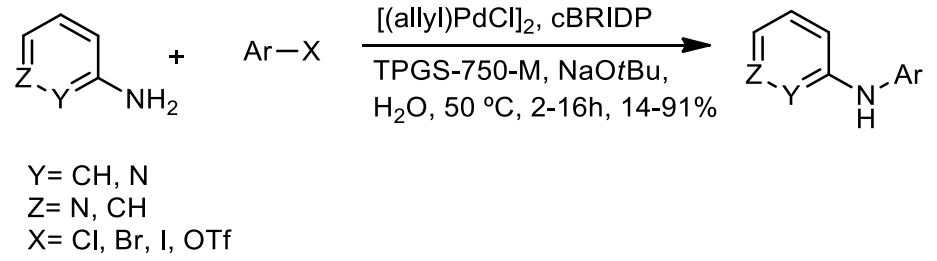
In 1999, Sakamoto and co-workers reported the first coupling of aminopyridines and iodobenzenes.[36] The group obtained the C–N cross-coupling products of 2-, 3- and 4-aminopyridines and the respective *ortho*-halo-substituted analogues with iodobenzenes, in moderate to high yields (Scheme 17). The catalytic system used was again Pd_2dba_3 and the ligand dppf (1,1'-Bis(difenilfosfino)ferrocen).



Scheme 17 – First C–N cross-coupling reaction of 2-, 3- and 4-aminopyridines with iodobenzenes[36].

A more recent and sustainable example consisted on the Pd catalyzed amination, under micellar conditions (TPGS-750-M), of several substrates, described by Salomé and co-workers in 2014.[37] This approach involved the coupling of 3-aminopyridine with aryl halides and triflates and 2-aminopyridine with 3-bromotoluene, in water, at 50 ºC (Scheme 18).

The authors obtained the corresponding products with yields between 14-91% using $[PdCl(allyl)]_2$ catalyst and monodentate ligand cBRIDP (Di-tert-butyl(2,2-diphenyl-1-methyl-1-cyclopropyl)phosphine). They expanded the scope of the work developed by Lipshutz and co-workers,[38] who created the surfactant that allows the milder conditions observed in the C–N cross-coupling reaction, by providing a lipophilic environment for high reagents concentration.



Scheme 18 – Sustainable C–N cross-coupling method for the synthesis of azaindoles from 2-, and 3-aminopyridine using surfactant conditions[37].

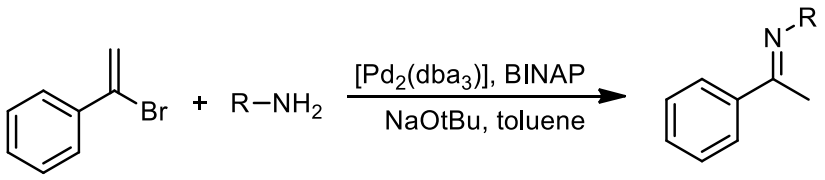
1.3.2. Synthesis of imine/enamine compounds

Enamines are valuable synthetic intermediates for organic synthesis,[39,40] and have gain special interest in the synthesis of azaindoles as their precursors (see *1.2.4* and *1.2.5*). However, the traditional strategy to obtain them, through ketone condensation with amines, requires harsh conditions, lacks selectivity and isn't suitable for many functional groups. Additionally, enamines/imines are prone to hydrolyses and, under condensation conditions, a water scavenger is often required.[41]

Remarkably, in 2002, Barluenga and co-workers described, for the first time, the intermolecular palladium-catalyzed cross-coupling reaction between secondary amines and alkenyl bromides, which afforded enamines in good yields and regioselectivity.[42] Later, in 2004,[43] the same group reported the detailed study of the scope and demonstrated that the method is very efficient for the preparation of imines/enamines, providing a strong contribution to the expansion of the palladium-catalyzed C–N cross-coupling reaction.

Among different types of amines and bromides, the group optimized the conditions of imine synthesis by coupling of a series of primary aniline derivatives with α-bromostyrene, using the catalytic system Pd_2dba_3/BINAP(2,2′-bis(diphenylphosphino)-1,1′-binaphthyl)/NaO*t*Bu, in toluene.

From 15 minutes up to 20 h of reaction, the group obtained imines in almost all in quantitative yields (Scheme 19). Other vinyl bromides were also tested, and the same results obtained.



R= *p*-OMe-Ph, *p*-Me-Ph, *p*-CN-Ph,
p-NO_2-Ph, *o*-Me-Ph, *o*-OMe-Ph,
o-Br-Ph, *m*-Br-Ph, *p*-Br-Ph,
Bu, Allyl, CH_2-*p*-OMe-Ph,
$CH(CH_3)$-Ph,
2,4,6-Me-Ph, 2,6-Br-Ph,

Scheme 19 –Optimized conditions for the synthesis of imines from primarily anilines and α-bromostyrene, using C–N cross-coupling reaction described by Barluenga *et. al.* [43].

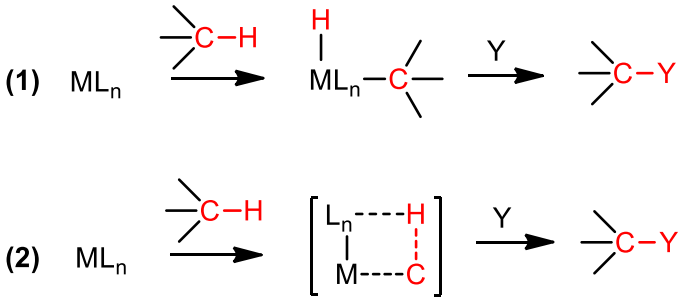
With these derivatives in hand, a new, facile route, towards the synthesis of various heterocycles,[44] particularly, azaindoles,[27,45] was open for organic chemists to developed.

1.4. The C–H activation/functionalization reaction

1.4.2. Principles and examples of C–H activation/functionalization

The C–H bond was thought to be a chemical bond unable to directly participate in chemical reactions but, despite of its very low reactivity, direct C–H bond activation/functionalization has emerged as a great approach to achieve all sort of chemical transformations without the need of traditional pre-functionalization of molecules, becoming also a target for economic and environmental chemistry.[46]

The terms C–H activation and C–H functionalization have been used in the literature interchangeably, due to the difficulty in determining the difference between the two. However, they are now being more distinguished by the mechanism of the reaction: the C–H activation occurs in *inner sphere* mechanism – there is a covalent coordination of the C–H bond to the metal center and no dissociation from the actual organic molecule, creating a new organometallic complex; while the C–H functionalization operates in *outer sphere* mechanism – the C–H bond inserts itself in the ligand of the metal complex. A basic example of these mechanisms is represented in Scheme 20.[46,47]

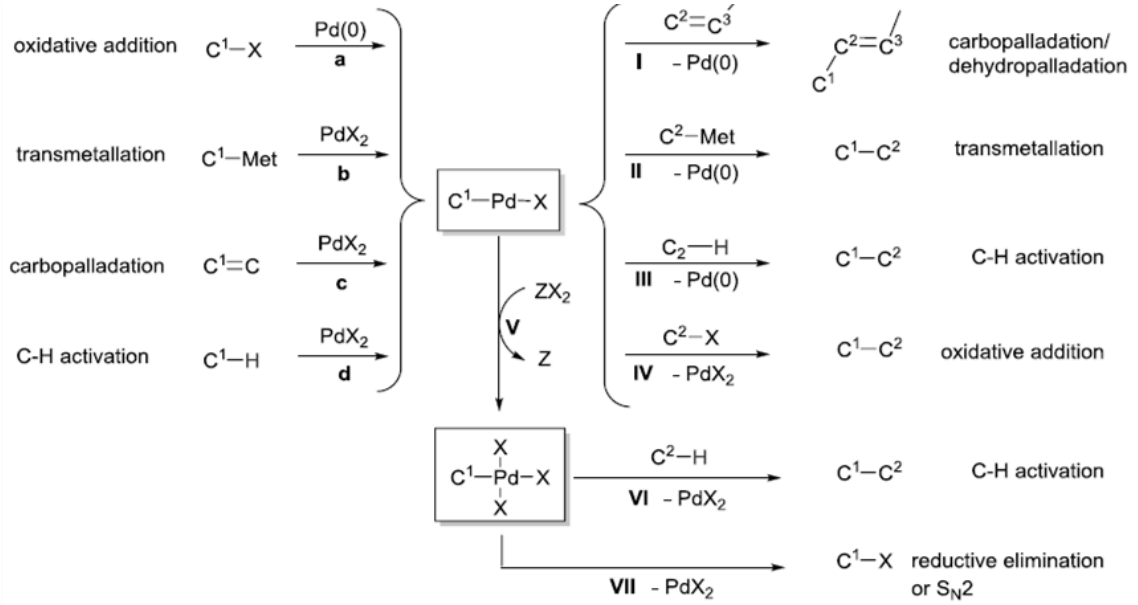


Scheme 20 – C–H activation **(1)** *inner sphere* mechanism; C–H functionalization **(2)** *outer sphere* mechanism.

Although the first examples of C–H activation/functionalization started as early as in the XIX century[48], Chatt can be regarded as the first one to report a C–H activation reaction, in 1965, by inserting a ruthenium(0) catalyst in a C–H bond of naphthalene.[49]

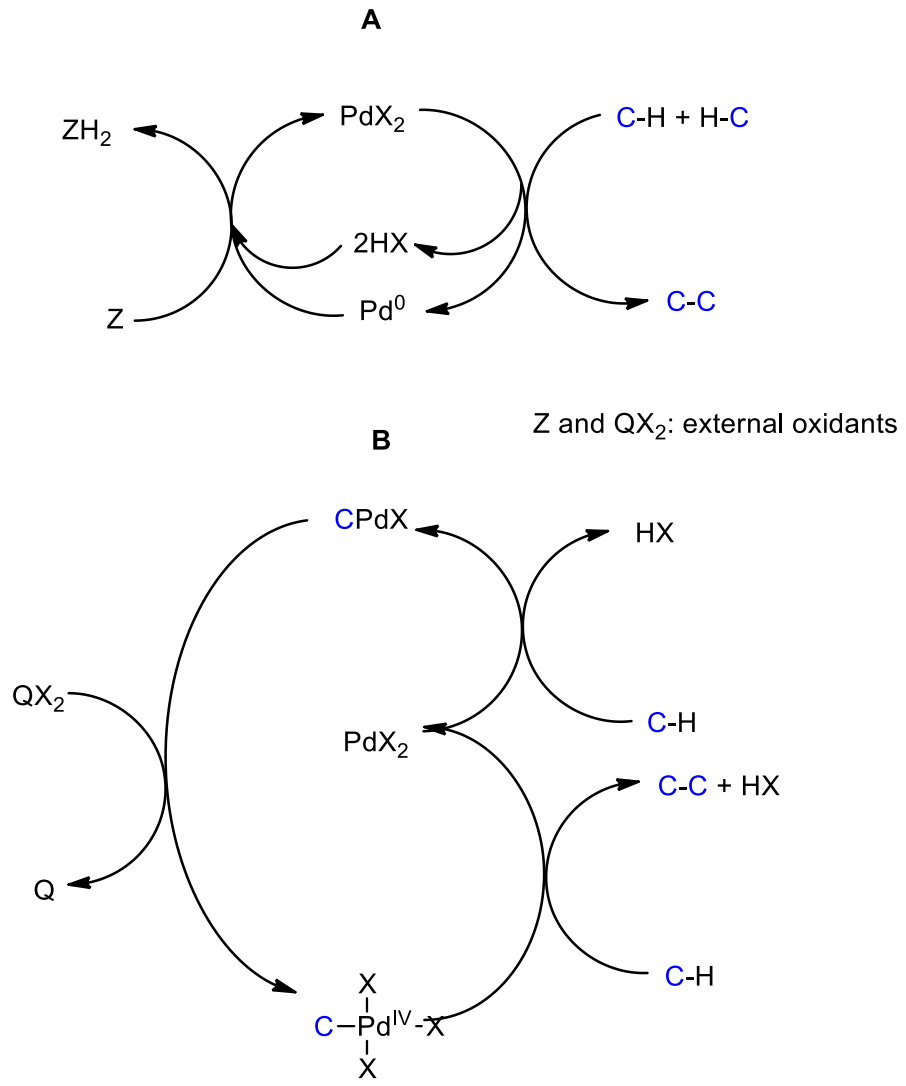
Since then, C–H activation has been extensively explored in all type of substrates and has become a part of the C–C bond formation cross-coupling reactions. In the context of sustainable and green chemistry, the most relevant type of C–H activation is the C–C bond formation via dual C–H activation.

This can be known as a cross dehydrogenative coupling (CDC) or dual C–H activation reaction. Specifically, in palladium-catalyzed C–C cross-coupling reactions (Scheme 21), this would correspond to paths **d – III** or **d – V – VI**. Curiously, even though most C–H activation reactions take place in palladium(II) oxidation state, a superior oxidation state caused by an external oxidant can occur (path **V**), and a palladium(IV) complex intermediate is achieved.[46,50]



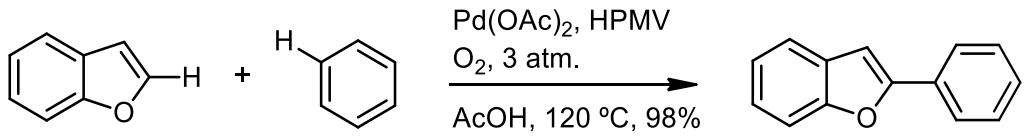
Scheme 21 – Palladium-catalyzed C–C cross-coupling reactions (figure adapted from literature).[46]

Since the C–H activation is an oxidative process, an external oxidant is required to close the catalytic cycle. Palladium(IV) species only occur when the oxidative process takes place before the product is formed (Scheme 22, B), if not, then the product is released and palladium(0) is formed before being restored to palladium(II) by the external oxidant (Scheme 22, A).[46]

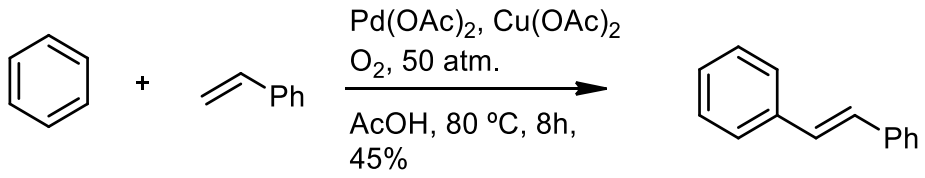


Scheme 22 – C–C bond formation from C–H activation mechanism. Pd^{II}/Pd^{0} in **A** and Pd^{II}/Pd^{IV} in **B**. Adapted from [46].

Among CDC type of C–H activation, a few important examples rely on aryl/aryl coupling (Scheme 23)[51] and aryl/alkene couplings (Scheme 24) [52]. Particularly, the palladium-catalyzed oxidative coupling of aryl/alkene is now known as the Fujiwara–Moritani reaction.



Scheme 23 – CDC hetero-coupling between benzofuran and benzene for a C–C bond formation disclosed by DeBoef[51].

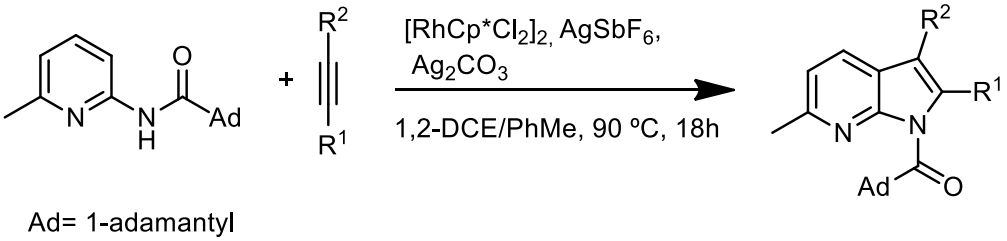


Scheme 24 – The Fujiwara–Moritani reaction disclosed in 1967 for the C–C bond formation from aryl and alkene coupling[52].

1.4.2. Azaindole synthesis via C–H activation

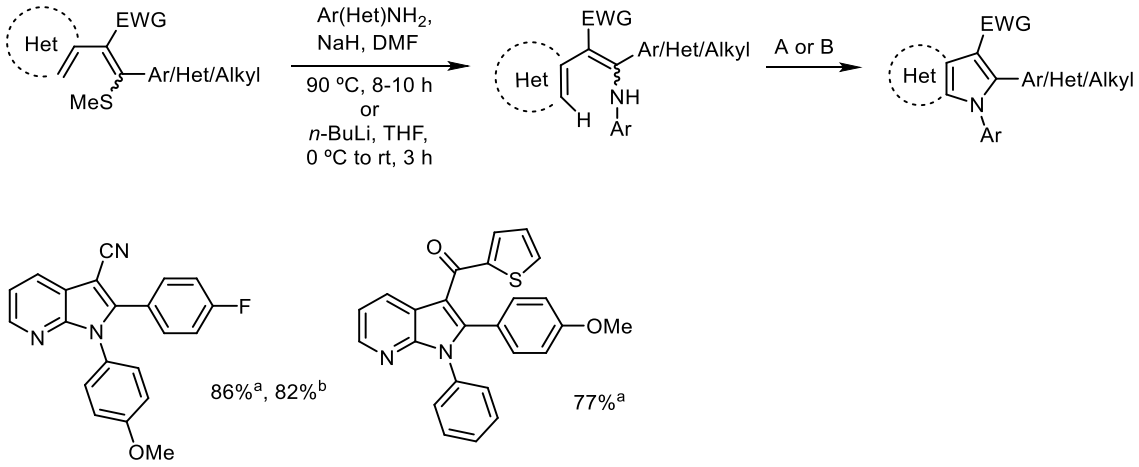
Despite of the various examples on C–H activation reaction applied to the synthesis of indole, [53] this approach has been scarcely investigated on the assembly of the azaindole core.

In 2015, Kim and co-workers developed a Rh(III)-catalyzed C–H activation/annulative coupling of aminopyridines with alkynes[54] (Scheme 25). The method proved highly efficient for the synthesis of 7-azaindole derivatives with a wide scope and functional group versatility. Yields were also satisfactory, varying between 46-94%. In the reaction, the group used Ag_2CO_3 as an additive to coordinate to the nitrogen in the pyridine moiety, proposing that the silver atom facilitated the C–H bond cleavage and, therefore the annulation process.



Scheme 25 –Synthesis of azaindoles from alkynes and N-substituted aminopyridines via C–H activation using a Rh(III) catalyst reported by Kim *et al.* [54].

Inspired by the work developed by Buchwald's group in 2005,[55] on the carbazole synthesis via Pd(II)-catalyzed intramolecular C–H activation/C–N bond formations, Yugandar *et al.*, in 2016[56], designed a strategy towards the synthesis of several heterocycles using a palladium-catalyzed intramolecular oxidative C–H functionalization–amination of readily available 2,3-(het)aryl-3-N-aryl/acylenaminonitriles and enaminones (Scheme 26). Among the products obtained, two azaindoles were synthesized in good yields using two different catalytic systems (A and B).



Scheme 26 – C–H activation synthesis of 7-azaindole core from 2,3-(het)aryl-3-*N*-aryl/acylenaminonitriles and enaminones by Yugandar *et al.* [56]. [a]Yield by A: $Pd(OAc)_2$ (20 mol%), $Cu(OAc)_2$ (1 equiv.), DMSO, O_2 atm, 120 °C, 8-10 h; [b]Yield by B: $Pd(OAc)_2$ (20 mol%), Ag_2CO_3 (1 equiv.), PivOH (1 equiv.), DMSO, O_2 atm, 120 °C, 10-12 h.

Despite of all efforts, the synthetic approaches mentioned are restricted to the 7-azaindole regioisomer.

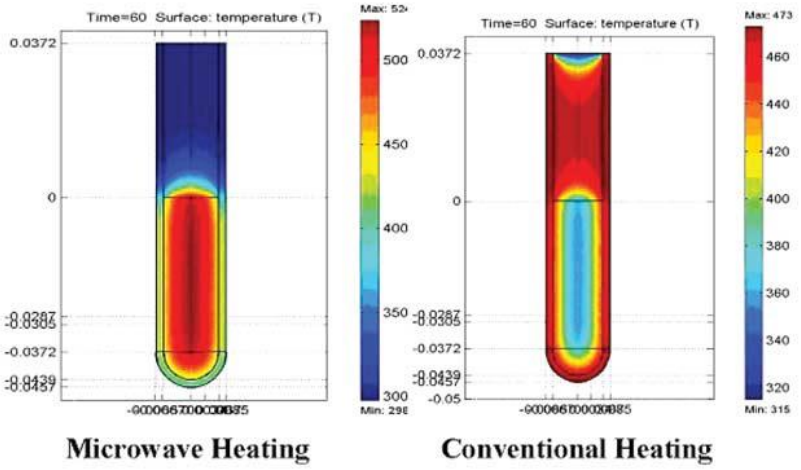
1.5. Microwave assisted reactions

1.5.1. Conventional heating vs microwave accelerated heating

In organic synthesis, reactions that are carried out thermally can be performed by either conventional heating or microwave accelerated heating. Microwave irradiation in organic synthesis was only introduced in 1986[57,58], but since then has been continually used in pharmaceutical and academic areas.

What differentiates microwave heating from conventional heating is, essentially, the way the reaction mixture is heated. Whereas in the first way, the heat has an external source and must pass through the walls of the vessel to heat the solvent and the reactants in a slow and less efficient way, microwave irradiation directly affects the molecules in the reaction mixture using a high frequency electric field. Under ideal conditions, the solvent or the reagent absorbs microwave irradiation and converts it into heat through molecular friction and dielectric loss.

Hence, there is no limitation from thermal conductivity of the vessel, and microwave heated systems become instantaneously superheated and present a distribution of heat much that is much more localized (Scheme 27).[59,60]

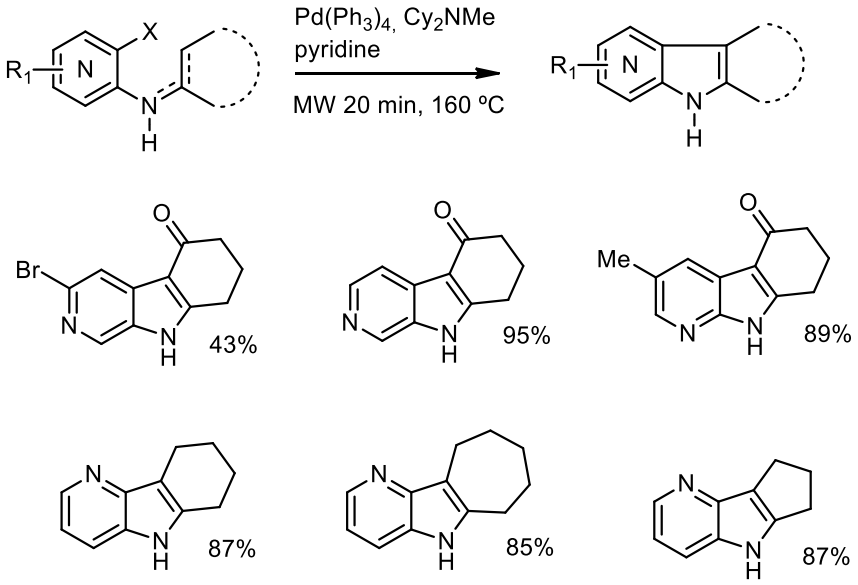


Scheme 27 – Heat distribution comparison between microwave heating and conventional heating (adapted form literature).[61]

1.5.2. Microwave heating in organometallic and azaindole synthesis

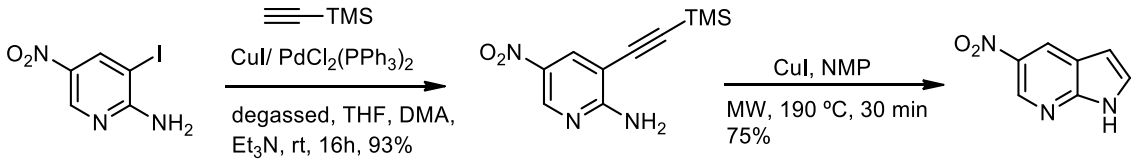
Microwave irradiation applied in metal-catalyzed organic chemistry has proved to improve traditional methods like the Sonogashira, Suzuki-Miyaura, Heck, Buchwald-Hartwig couplings and the C–H activation in a variety of substrates.[59,62] Still, regarding the synthesis of azaindoles through metal-catalyzed approaches, the literature is scarce. Some research groups were able to avoid the long reaction times required for this type of compounds, maintaining reasonable yields, although using elevated temperatures during the microwave irradiation.

As mentioned in Section 1.3.2, imines are key intermediates in organic synthesis. In 2005, Lachance and his group developed a one-pot method where, under microwave irradiation, amino-*ortho*-halogenated pyridines were condensed with ketones to form the respective imine/enamine intermediate. Subsequent palladium-catalyzed Heck reaction produced 4-, 5-, 6- and 7-azaindoles.[63] In 20 minutes of reaction at 160ºC, the authors obtained a protocol compatible with the presence of bromine, ketone and ester groups in the aminopyridine substrate and yields up to 95% (Scheme 28).



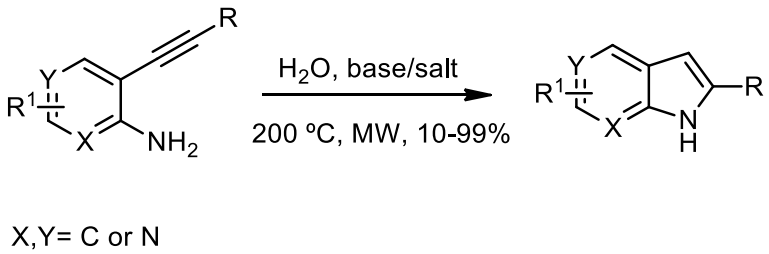
Scheme 28 – Lachance microwave heating aided palladium-catalyzed Heck reaction for the synthesis of azaindoles[63].

In the same year, Pearson and Nandan investigated the microwave assisted copper-mediated cyclization to achieve 5-amino-7-azaindole from a Sonogashira reaction product with the nitro-substituted aminopyridine.[64] The authors found that cyclization to the azaindole structure using catalytic CuI under 30 minutes of microwave irradiation at 190 ºC gave cleaner products, as oppose to the 16 hours of thermal heating under reflux (Scheme 29).



Scheme 29 – Pearson's Sonogashira copper-mediated cyclization using microwave heating for the syntheses of azaindoles[64].

In 2010 Ribecai and co-workers reported a microwave-assisted synthesis of indole and azaindole derivatives using 2-alkynylanilines and alkynylpyridinamines.[65] The reaction consisted on a cycloisomerization in water, that is promoted by catalytic amounts of neutral or basic salts or by stoichiometric weak organic bases (Scheme 30). The group also tested the results against thermal heating conditions which showed that microwave irradiation was necessary to obtain significant yields for shorter reaction times.



X,Y= C or N

Scheme 30 –Microwave-assisted synthesis of indole and azaindole derivatives using 2-alkynylanilines and alkynylpyridinamines reported by Ribecai *et al.* [65].

This chapter covered microwave-assisted reactions that are considered a green and sustainable alternative to the conventional oil-bath heating. It is still important to highlight that investigations about the energy efficiency of this method point to a decrease as the scale of the reaction increases, and that not all reactions will be automatically green as one applies microwave heating. Because of this, conventional heating can still be more energy efficient for industries. However, in terms of time efficiency, microwave assisted reactions are very useful for investigation purposes, offering several substrates in equal or improved yields, versus the thermal heating, in a fast way. To conclude, assessing energy and time efficiency is always recommended and depending on the purposes of the experiment, both conventional heating and microwave heating can be appropriate.[62]

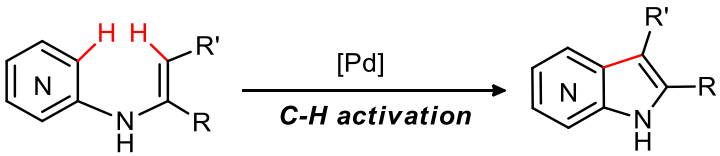
Chapter 2 – Results and Discussion

2.1. Background

As demonstrated in *Chapter 1*, azaindoles represent a major class of compounds with an extremely important role in biological and material sciences. However, these heterocycles appear to be synthetically challenging and difficult to achieve, which stimulates synthetic organic chemist to find new, clean and effective ways to attain this nucleus.

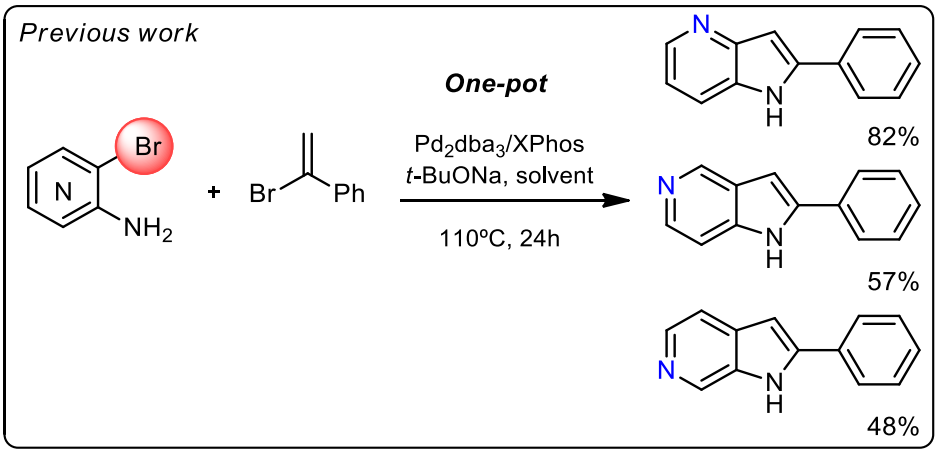
The previous Sonogashira reaction and the cascade C−N cross-coupling/Heck reaction approaches developed in our research Lab (See *1.2.1* and *1.2.5*, respectively), stimulated us to explore a C−H activation reaction to prepare azaindoles, that, opposed to the previous work, does not require any additional functionalization of the substrates, reducing cost and increasing the atom economy of the reactions. Particularly, the fact that almost all reactions must have halogenated substrates and that halogenation of aminopyridines has low regioselectivity[22], constitutes a problem that research groups are trying to improve[66,67] but can be avoided using this approach.

However, attaining azaindoles using the reactivity of carbon-hydrogen bonds represents a current synthetic challenge, as there are only two cases reported in the literature[54,56], limited to 7-azaindole. Indeed, the reactivity of aminopyridines in C−H activation reactions remains almost unexplored. Hence, we envisioned an intramolecular C−H activation reaction using imines/enamines intermediates that would allow a facile access to the azaindole core (Scheme 31).



Scheme 31 − C−H activation reaction envisioned from imine/enamine intermediates.

To obtain these imines/enamines intermediates, we resorted to our group experience regarding the C−N cross-coupling reaction of *ortho*-halo-aminopyridines and *α*-bromostyrene[27] that originated the respective azaindoles through cascade Heck reaction (Scheme 32).



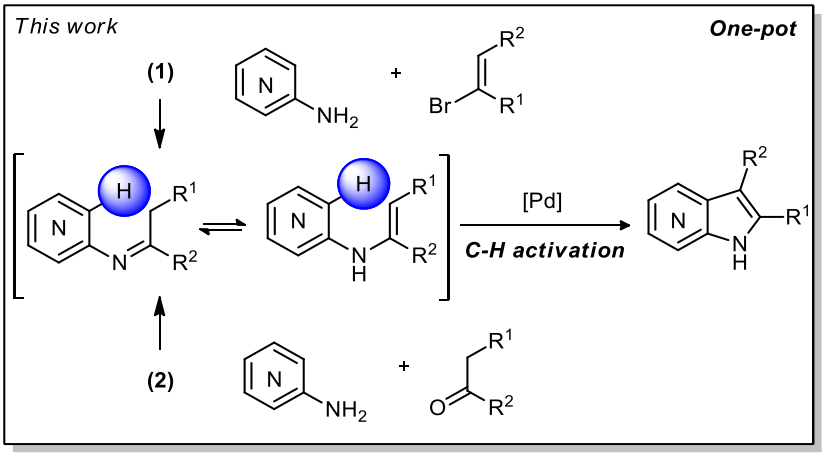
Scheme 32 − Azaindoles synthesized in our group previous work from ortho-halo-aminopyridines and *α*-bromostyrene, through a cascade C−N cross-coupling/Heck reaction.

Despite of the lower nucleophilicity of the amino group in aminopyridines relative to anilines, as well as their basicity and propensity to coordinate with metals, there has been as increasing development of metal-catalyzed C–C and C–N bond forming reactions strategies to allow aminopyridines functionalization. In our previous work (Scheme 32) several azaindoles were prepared from halogenated aminopyridines up to 82% yield. The work initiated with the reaction of halo-aminopyridines with *α*-bromostyrene to form the corresponding imines/enamines via C–N cross-coupling reaction catalyzed by palladium.

Thus, this work aimed to investigate the reactivity of aminopyridines and consequently develop a methodology to attain the azaindole core through palladium catalyzed C−N cross-coupling/C−H activation reaction from non-halogenated aminopyridines (Scheme 33 − 1).

Among this process, the use of microwave conditions was also tested. As seen in *Subchapter 1.5* microwave irradiation can be used to aid the synthesis of azaindole substrates but, also, it was described by various authors to successfully soften conditions, reduce reaction times and avoid side reactions, while maintaining moderated to excellent yields, specifically in C−N cross-coupling[68] and C−H activation/functionalization reactions[69].

Additionally, since alkenyl bromides are commercially limited to a few examples and have often to be synthesized, we envisioned a method to obtain the same enamine/imine intermediate through condensation of ketones and aminopyridines. Hence, a ketone condensation/ C−H activation was envisioned as a methodology to also attain the azaindole core (Scheme 33 – 2).

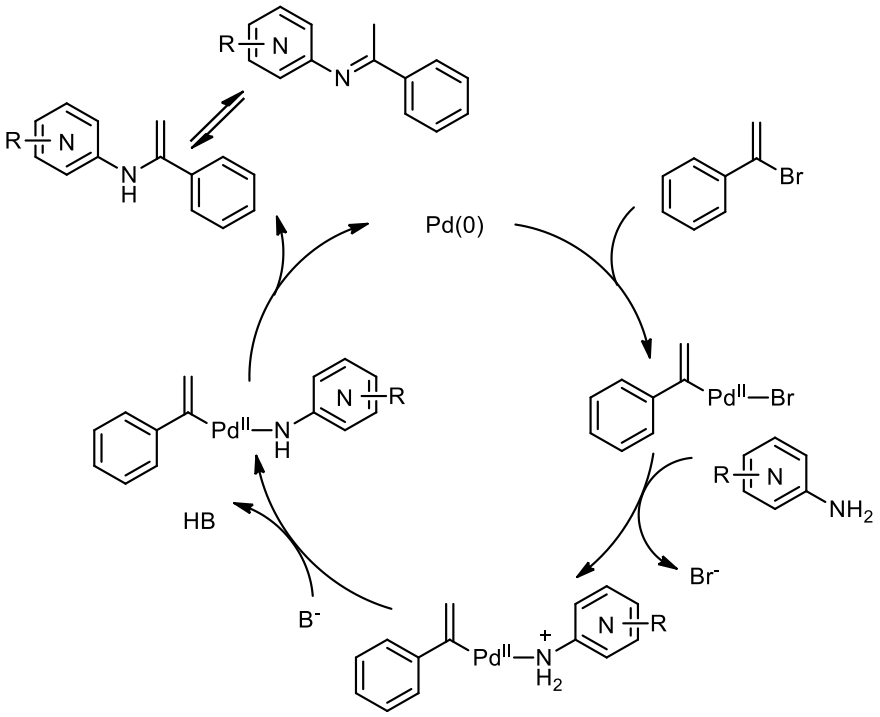


Scheme 33 − Proposed work to be developed in this master project.

2.2. Azaindole synthesis via palladium-catalyzed C−N cross-coupling/C−H activation reaction

Our previous exerience on the formation of imine/enamine intermediates via palladium-catalyzed C−N cross-coupling reaction, led us to explore a one-pot reaction of C−N cross-coupling /C−H activation between aminopyridines and alkenyl bromides, in order to obtain the azaindole.

The C−N cross-coupling reaction mechanism has been extensively studied, hence the catalytic cycle for *α*-bromostyrene and an aminopyridine can be represented as in Scheme 34.



Scheme 34 − Catalytic cycle for palladium-catalyzed C–N cross-coupling reaction of aminopyridines and *α*-bromostyrene.

The reaction initiates with an oxidative addition of the palladium(0) catalyst to the C–Br bond of *α*-bromostyrene, forming a palladium(II) complex that subsequently reacts in a nucleophilic substitution reaction with the aminopyridine substrate. A strong base deprotonates the aminopyridine and final reductive elimination reaction originates the new C−N bond, forming the enamine product and regenerating the palladium(0) catalyst. Tautomerism of the enamine can originate the imine. The specific delocalization of the equilibrium will depend on the relative stability of both tautomers in the reaction conditions.

The plan consisted of using the generated intermediate, without further manipulation, directly in a second catalytic reaction mediated by palladium(II) for the C−H activation/functionalization step, which would originate the azaindole. As this reaction is mechanistically more complicated and not yet completely established, hypothesis regarding its mechanism will be discussed further on. Additionally, to facilitate understanding, it'll be referred only as an activation reaction from here on.

2.2.1. Establishing the reaction conditions for the one-pot C−N cross-coupling/C−H activation reaction

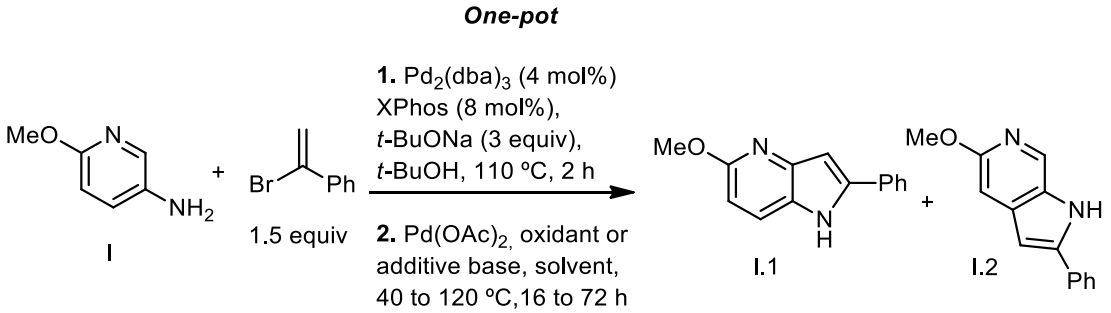
First experiments were performed using the catalytic system of the C−N cross-coupling reaction reported by us: $Pd_2(dba)_3$/XPhos(2-Dicyclohexylphosphino-2′,4′,6′-triisopropylbiphenyl)/*t*-BuONa system in *t*-BuOH [27].

Previous experiences performed in the laboratory suggested that an activating group in the azaindole moiety, such as the methoxy group, might counterbalance the electronegativity of the pyridine moiety and make the aminopyridine more reactive. Thus, the optimization of the reaction conditions was performed with 5-amino-2-methoxypyridine (aminopyridine **I**) and *α*-bromostyrene, as the latter was successfully applied in the C−N cross-coupling reaction of our group work on C−N cross-coupling /Heck reactions.

Enamine/imine formation was detected through TLC analysis with the aid of the Ehrlich's reagent dye. Since the procedure is one-pot, after completion of the C−N cross-coupling reaction, which was monitored via TLC, the solvent was evaporated to dryness and no further manipulation was done. For the C−H activation, $Pd(OAc)_2$ was used has the catalyst, and different oxidants, additives, bases and solvents were tested (Table 1).

First it was ascertained if a base or an additive were necessary to obtain good results. However, in the absence of any of these entities, a large loading of catalyst and oxidant (3 and 6 equiv.) was necessary to obtain the azaindole in a reasonable yield (Table 1 – entry 2).

Table 1 – Table of optimization of the reaction conditions for the C−N cross-coupling /C−H activation reaction.



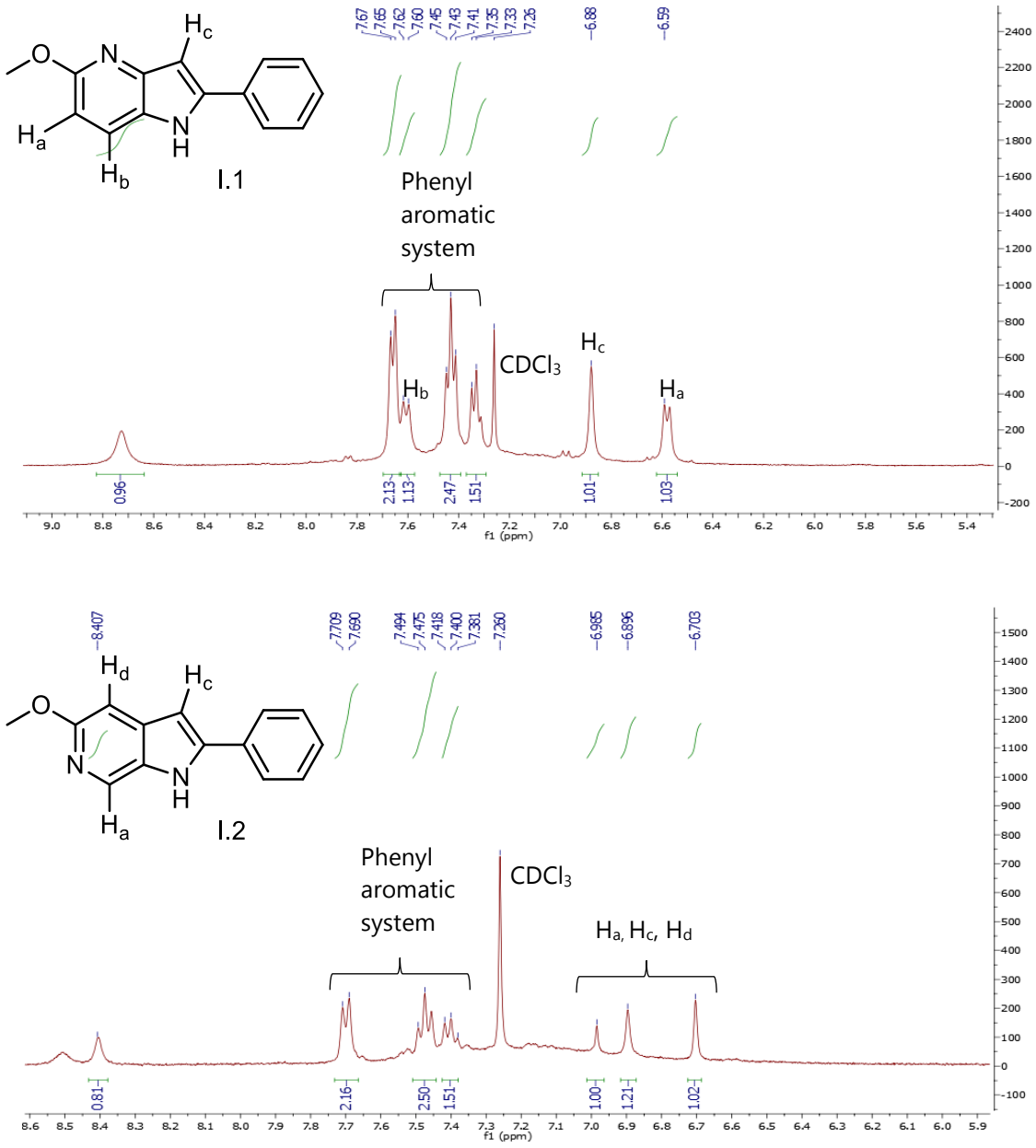
Entry	Pd cat. Step 2 (mol%)	Base/Additive[a]	[Ox] (equiv.)	Solvent	I.1 Yield (%)	I.2 (%)
1	$Pd(OAc)_2$ (10)	-	$Cu(OAc)_2$ (3)	DMSO	19	trace
2	$Pd(OAc)_2$ (20)	-	$Cu(OAc)_2$ (6)	DMSO	41	trace
3	$Pd(OAc)_2$ (10)	TBAB	$Cu(OAc)_2$ (3)	DMSO	trace	-
4	$Pd(OAc)_2$ (10)	TBAB	O_2	DMSO	trace	-
5	$Pd(OAc)_2$ (10)	K_2CO_3	$Cu(OAc)_2$ (3)	DMSO	45	-
6	$Pd(OAc)_2$ (10)	K_2CO_3	$Cu(OAc)_2$ (3)	DMF	-	-
7	$Pd(OAc)_2$ (10)	Ag_2CO_3	$Cu(OAc)_2$ (3)	DMSO	17	19
8	**$Pd(OAc)_2$ (10)**	**Cs_2CO_3**	**$Cu(OAc)_2$ (3)**	**DMSO**	**49**	**9**
9[b]	$Pd(OAc)_2$ (10)	Cs_2CO_3	$Cu(OAc)_2$ (3)	DMSO	10	4
10[c]	$Pd(OAc)_2$ (20)	PivOH	Ag_2CO_3	DMSO	16	16
11	-	-	-	DMSO	-	-
12	-	Cs_2CO_3	-	DMSO	-	-

[a]All experiments were carried with 3 equiv.; [b]Step 1 was carried using XantPhos as ligand. [c]1 equiv. of PivOH was used.

To avoid using these quantities, a phase transfer catalyst (TBAB) was used, in order to see if there were solubility issues that affected the reaction outcome. However, no improvement was observed, and direct oxygenation of the reaction mixture also didn't provide better results (Table 1 – entries 3 and 4).

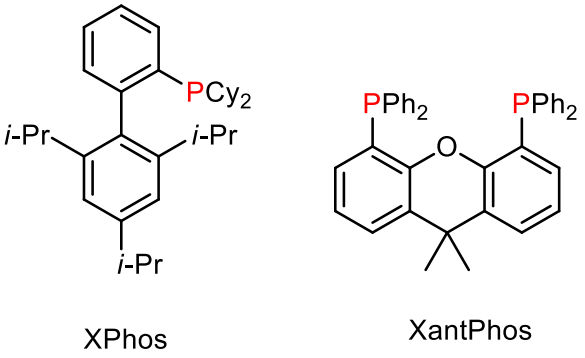
Hence, K_2CO_3 as a base was tested, and a satisfactory yield of azaindole **I.1** was observed using 3 equiv. of $Cu(OAc)_2$ and 10 mol% of palladium catalyst. This indicated that a base is necessary for the reaction to provide significant yields. With these results is hand, DMF was tested as a solvent instead of DMSO, but, curiously, no azaindole formation was observed (Table 1 – entries 5 and 6).

Finally, Cs_2CO_3 as a base provided the best yields (Table 1 – entry 8). In this essay considerable amounts of the corresponding azaindole were obtained that enabled the identification of isomer **I.2** by ^1H NMR, as the product of cyclization at C-4 position of the aminopyridine. The spectra obtained had a significantly different distribution of signals from the aromatic protons of the aminopyridine ring. As illustrated in Scheme 35, in isomer **I.1**, protons H_a and H_b are coupling partners, which translates into two duplet signals integrating to 1 hydrogen each; in isomer **I.2** however, the ring formed between protons H_a and H_d, that do not feel each other's magnetic field, which originated two distinct singlets.



Scheme 35 – Azaindoles isomer **I.1** and **I.2** ^{1}H NMR comparison in $CDCl_3$. Distinct difference in the signals relative to the aromatic system of the aminopyridine ring.

We wondered if the imine/enamine formation could be a limiting step in the sequence. Thus, we decided to turn back our attention to the C–N cross-coupling reaction and perform further studies to optimize this step using this aminopyridine. For this purpose, the XPhos (Scheme 36) ligand was switched to a bidentate phosphine ligand XantPhos (Scheme 36) (Table 1 – entry 9). The bulkiness of the resulting catalyst should further protect the metal center from pyridine coordination comparing with the monodentate XPhos, avoiding a possible catalyst poisoning. However, the essay revealed a drastic reduction of yield. This indicated that there was a difficulty in achieving the imine/enamine intermediate under these conditions, which is most likely due to steric hindrance issues regarding aminopyridine approximation to the catalyst.



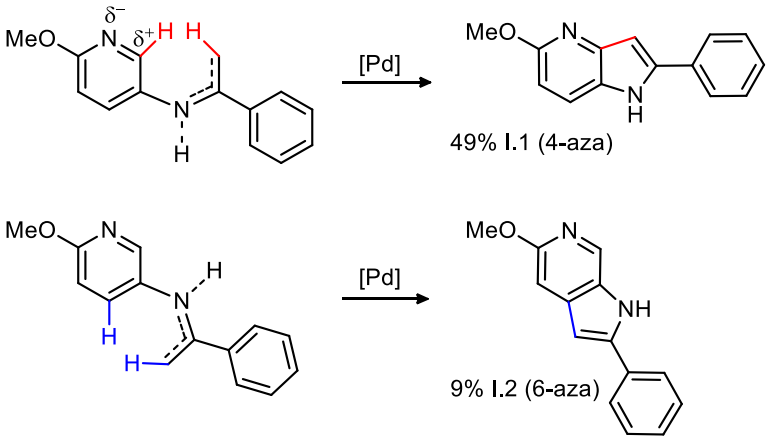
Scheme 36 – XPhos and XantPhos structures. Red indicates the atom that coordinates to the metal center.

A different catalytic system consisting of $Pd(OAc)_2/Ag_2CO_3$/PivOH was also tested (Table 1 – entry 10). A similar condition was reported by Yugandar *et.al.* for a C–H activation reaction towards azaindole synthesis.[56] The use of silver salts in the reaction has the purpose of reducing the basicity of aminopyridines by silver coordinating to the nitrogen in the pyridine ring, therefore avoiding catalyst poisoning.[54] Even so, the yields obtained did not improve. However, the isomers of the azaindole were obtained in similar amounts. A similar result was observed when Ag_2CO_3 was used as the base of the reaction (Table 1 – entry 7).

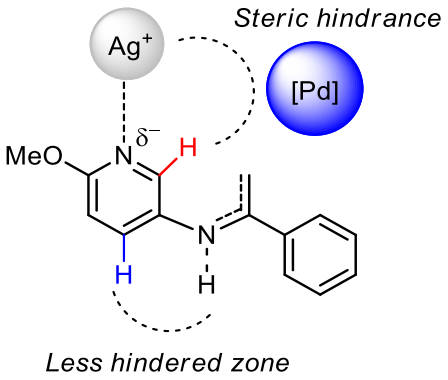
These results gave us an important insight to the selectivity of the reaction regarding the two C–H bonds that can undergo activation in aminopyridine **I**.

2.2.2. The selectivity of the C−H activation reaction

Without a silver additive system, we observe that the major product of the reaction is formed via the C–H bond adjacent to the nitrogen in the pyridine ring (C-2) and the 4-aza isomer **I.1** is the major product (Scheme 37).



Scheme 37 – C–H bonds that undergo C–H activation reaction in aminopyridine **I** under $Pd(OAc)_2/Cs_2CO_3/Cu(OAc)_2$ catalytic system.



Scheme 38 – Silver salt coordination in imine/enamine intermediate reduces pyridine basicity and affects the selectivity of the C–H activation.

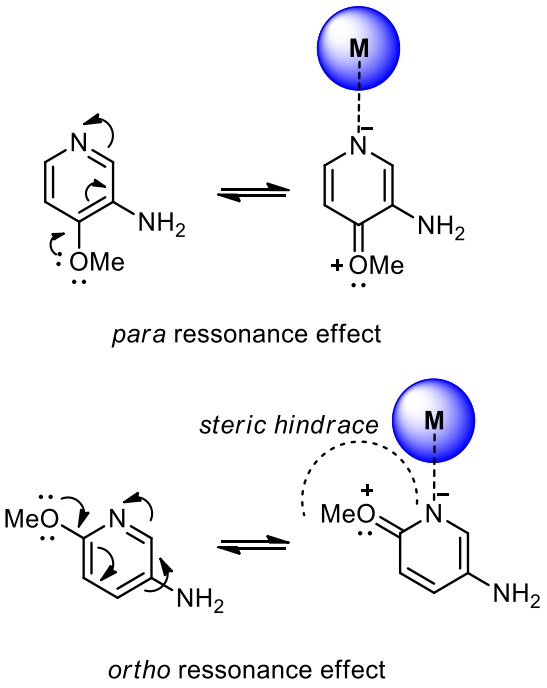
This can be due to the electronegative affect that the nitrogen in the pyridine ring has on the adjacent C−H bond strength. When no silver is present, this effect is most noticeable, and the C-4 position is more polarized, facilitating the palladium catalyst insertion. However, when silver is added, the electronegativity of the nitrogen in the pyridine ring is attenuated and the adjacent C-H bond is less affect, hence, there is no longer such a difference in reactivity between the two C-H bonds that can undergo activation. Additionally, the favored formation of this isomer might also be due a steric hindrance effect taking place from silver blocking palladium approximation to the C−H bond adjacent to the nitrogen in the pyridine ring (Scheme 38), therefore reducing isomer **I.1** yield while increasing isomer **I.2**.

2.2.3. Testing and optimizing the reaction for 3-amino-4-methoxypyridine (II)

Having established the reaction conditions for aminopyridine **I** and *α*-bromostyrene, we decided to experiment with 3-amino-4-methoxypyridine (aminopyridine **II**) since it was also activated by the methoxy group.

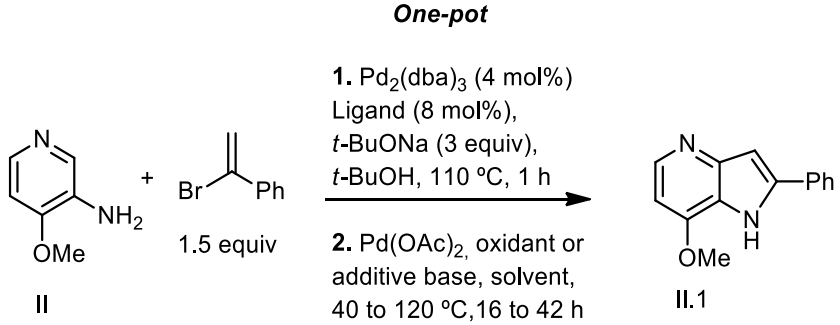
Contrarily to aminopyridine **I**, which has a methoxy group in *ortho* position to the nitrogen and must enforce some steric hindrance that naturally prevents it's coordination to the metal (as seen when the yields lowered in the essays with XantPhos and silver salts, Table 1 – entries 9 and 10) aminopyridine **II** isn't quite the same case. We suspected that this aminopyridine could have a more intense binding to the metal catalyst, poisoning this one, since the resonance of the methoxy group in *para* position significantly increases the pyridine basicity. Additionally, the nitrogen of the pyridine is completely available for coordination to the metal in a steric hindrance perspective, comparingly to aminopyrine **I** (Scheme 39).

Thus, we decided to test with XantPhos in the C−N cross-coupling reaction and $Pd(OAc)_2/Ag_2CO_3$/PivOH catalytic system for the C−H activation reaction. Gratefully, these reaction conditions resulted in 37% yield (Table 2 – entry 1).



Scheme 39 – Methoxy group effect in the coordination of the pyridine ring to the metal catalyst from 3-amino-4-methoxypyridine and 5-amino-2-methoxypyridine.

Table 2 – Testing of the reaction conditions for the C–N cross-coupling and C–H activation reaction for aminopyridine **II**.



Entry	Substrate	Ligand	Pd. cat. (mol%)	Additive (equiv.)	[Ox] (equiv.)	Azaindole Yield (%)
1	**II**	XantPhos	$Pd(OAc)_2$ (20)	PivOH (1)	Ag_2CO_3 (1)	37
2	**II**	XantPhos	$Pd(OAc)_2$ (20)	$CsCO_3$ (3)	$Cu(OAc)_2$ (3)	Trace
3	**II**	XPhos	$Pd(OAc)_2$ (20)	PivOH (1)	Ag_2CO_3 (1)	Trace

To ascertain if both the ligand XantPhos and Ag_2CO_3 were necessary in the catalytic system to favor the reaction outcome, essays 2 and 3 were performed. When XPhos was used in the C–N cross-coupling reaction with the $Pd(OAc)_2$/PivOH/Ag_2CO_3 catalytic system (Table 2 – entry 3), only trace amount of azaindole was detected. Additionally, when XantPhos was used in the C–N cross-coupling reaction with the $Pd(OAc)_2$/$Cu(OAc)_2$/Cs_2CO_3 catalytic system (Table 2 – entry 2), also only trace amount of azaindole was formed. These results led us conclude that only the combination of the XantPhos protection of the catalyst in the C−N cross-coupling reaction and the effect of silver in reducing the nucleophilicity of the pyridine ring in the C−H activation reaction can offer a reasonable yield for azaindole **II.1**.

The polarization effect of silver seen for aminopyridine **I** in the C−H bond is less noticeable in aminopyridine **II** because there's only one C−H bond that can undergo activation, so we still have the azaindole product, even though the bond is less polarized. However, there is only one isomer forming in this aminopyridine, so this effect can also explain the lower yield this substrate has for the azaindole product, comparing to the 32% conversion of azaindole for aminopyridine **I** that has two isomers forming.

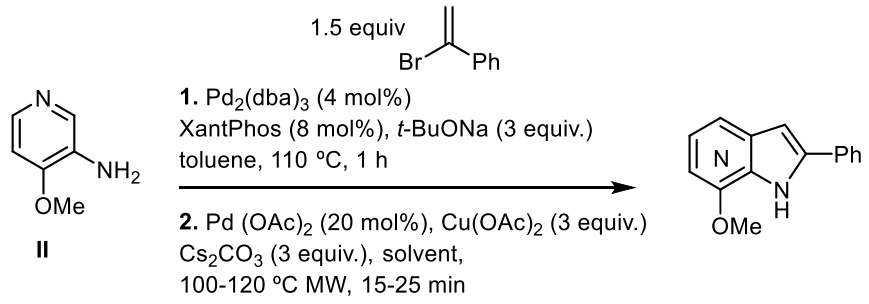
2.2.4. Microwave-assisted reactions

Given the fact that these reactions take several hours to complete, and yields could still be improved, we decided to experiment the C−N cross-coupling /C−H activation with microwave irradiation.

We first evaluated if another solvent could be used in the C−H activation step compatible with microwave conditions, since DMSO had some disadvantages in the work-up process. Given its high boiling point, it cannot be properly evaporated from the reaction mixture and it is required to perform extractions in order to remove it from the crude, which drags some product to the aqueous phase and reduces yields.

We already knew that dimethylformamide (DMF) was not an option since no azaindole formation was observed during the optimization process (Table 1 – entry 6). We decided to try under microwave conditions with acetonitrile (ACN), but, again, there was no azaindole formation (Table 3 – entry 1). A 5:2 mixture of ACN/DMSO (Table 3 – entry 2) was also tested and, curiously, azaindole was immediately detect through TLC analysis. This was an indication that DMSO might be crucial for the reaction to occur. Employing only DMSO as the solvent (Table 3 – entry 3) also resulted in formation of the azaindole.

Table 3 – Exploring solvents for the C−H activation reaction of imine/enamine intermediate of aminopyridine **II**.



Entry	Solvent Step 2	Yield
1	ACN	-
2	ACN/ DMSO (5:2)	Trace amount
3	DMSO	Trace amount

After evaluating the solvent for the C−H activation reaction, we decided to explore the optimized conditions established in the thermal heating method using microwave irradiation instead (Table 4). We immediately found that the C−N cross-coupling reaction was extremely efficient using microwave conditions. The reaction of both aminopyridines **I** and **II** was complete to afford the imine/enamine, by TLC analysis, in just 15min at 110 ºC of irradiation, as oppose to the 1 h-2 h of 110 ºC in conventional thermal heating.

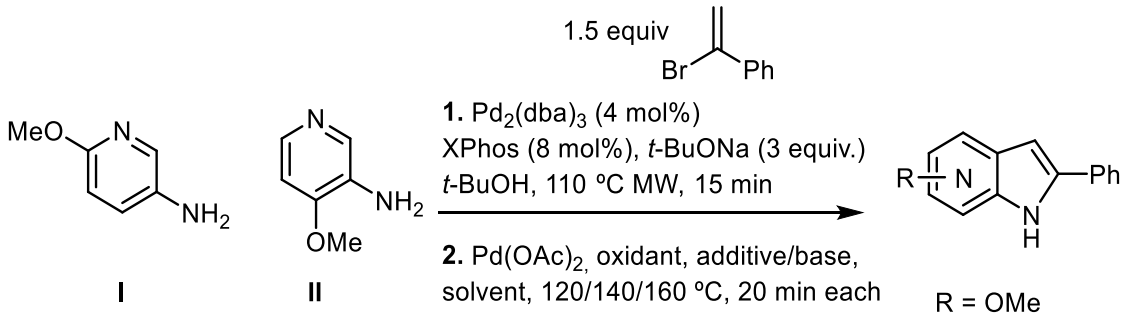
However, contrarily to the thermal heating procedure, microwave conditions required the use of a specific vial that didn't allow facile evaporation of the solvent used in the first step of the reaction, without direct manipulation of the reaction mixture. Hence, we decided to test a biphasic solvent (1:1), adding the solvent of the second step of the reaction along with the respective catalytic system and observe azaindole formation and the corresponding yield (Table 4 – entries 1 and 2). Unfortunately, the biphasic solvent (1:1) conditions afforded trace amount of the azaindole. Given that the major difference was the fact that we had a biphasic solvent in the C−H activation step, we assumed that the reaction wasn't favorable under these conditions, either due to solubility issues from having two solvents instead of just DMSO or by having a completely different concentration of the reactants, since more than double the amount of solvent was being used in the biphasic essays.

From here we decided to follow the procedure with removal of the solvent of the first step, expecting the results to be somewhat similar to the ones in thermal heating conditions. Yet again, only trace amount of azaindole was formed, for both aminopyridines (Table 4 – entries 3 and 4).

Finally, we realized that the concentration of the reaction might be the issue affecting the yields, since the specific vials required for the reaction also had specific volumes of solvent necessary for the equipment to function. Because of this, we had a concentration of 0,05M in microwave conditions instead of the 0,1M from thermal heating conditions. Has mentioned previously, DMSO must be extracted with water during the work-up of the reaction before we can proceed with column purification.

The only way to explain the poor results obtained is through massive loss of product in the extractions performed, which is easy to perceive given the concentration of the product in the crude. We concluded that the C−H activation step wasn't viable in microwave conditions.

Table 4 – Testing of microwave conditions for one-pot, biphasic solvent solution, for aminopyridines I and II.



Entry	Substrate	Solvent Step 1	Pd cat. (mol%)	Additive (equiv.)	[Ox] (equiv.)	Solvent Step 2	Yield
1	**I**	*t*-BuOH	$Pd(OAc)_2$ (10)	Cs_2CO_3 (3)	$Cu(OAc)_2$ (3)	DMSO	Trace amount
2	**II**	*t*-BuOH	$Pd(OAc)_2$ (20)	PivOH (1)	Ag_2CO_3 (1)	DMSO	Trace amount
3[b]	**I**	*t*-BuOH	$Pd(OAc)_2$ (10)	Cs_2CO_3 (3)	$Cu(OAc)_2$ (3)	DMSO	Trace amount
4[b]	**II**	*t*-BuOH	$Pd(OAc)_2$ (20)	PivOH (1)	Ag_2CO_3 (1)	DMSO	Trace amount

The ligands used in the C−N cross-coupling reaction were XPhos and XantPhos for aminopyridine **I** and **II**, respectively. [a]Biphasic conditions. [b]Solvent from step 1 was evaporated to dryness before step 2.

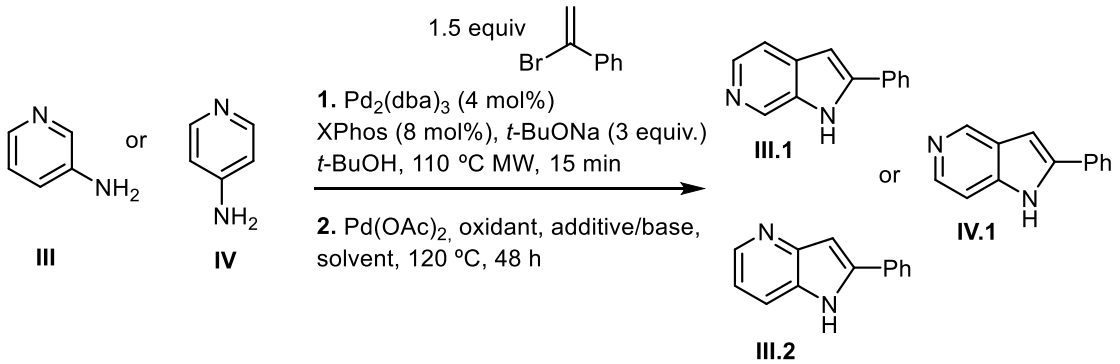
2.2.5 Introduction to non-activated aminopyridines

For some time, it was thought that the activating group (the methoxy group) was a requisite to perform the C−N cross-coupling /C−H activation reaction, since previous studies in the laboratory with unsubstituted aminopyridines failed to provide the imine/enamine intermediate (4-aminopyridine) or didn't provide considerable amounts of azaindole (3-aminopyridine). This could be due to a weak C−N cross-coupling reaction, since the amine from the pyridine needs to be nucleophilic enough to engage in nucleophilic substitution with the palladium catalyst.

However, given the success microwave irradiation had on the C−N cross-coupling reaction for aminopyridines **I** and **II**, we decided to try these conditions for 3- and 4-aminopyridines (aminopyridines **III** and **IV**, respectively). Delightedly, we observed that under microwave heating at 110 ºC, both aminopyridines underwent enamine/imine formation as good as their activated analogues.

For the C−N cross-coupling reaction, we decided to use the optimized conditions for aminopyridine **I**, with XPhos as the chosen ligand. The reaction proceeded smoothly and was completed (through TLC analysis) after the expected 15 min of irradiation at 110 ºC MW. The C−H activation reaction step was executed using thermal conditions (to avoid the excess DMSO problem discussed above) after solvent from step 1 was evaporated.

Table 5 – Testing of microwave conditions (C−N cross-coupling) combined with thermal heating conditions (C−H activation), for aminopyridines **III** and **IV**.



Entry	Substrate	Pd cat. (mol%)	Additive (equiv.)	[Ox] (equiv.)	Solvent Step 2	Azaindole Yield (%)
1	**III**	$Pd(OAc)_2$ (20)	PivOH (1)	Ag_2CO_3 (1)	DMSO	18 (**III.2**) 64 (**III.1**)*
2	**IV**	$Pd(OAc)_2$ (20)	PivOH (1)	Ag_2CO_3 (1)	DMSO	5 (**IV.1**)

*Pure by TLC analysis, ^{1}H NMR was difficult to obtain.

The total conversion of aminopyrine **III** into the respective azaindoles was the higher for these reactions, with a total of 82% yield for both isomers (Table 5 – entry 1). This result, when compared with the 32% total conversion in aminopyridine **I**, under the same reaction conditions (Table 1 – entry 10), suggests that the absence of the methoxy group is beneficial in the C–H activation step. This is in accordance with the fact that a more polarized C–H bond is easier for the insertion of the palladium catalyst, and since the methoxy group balances the electronegative effect of the nitrogen in the pyridine ring, the C–H bond is also less activated in aminopyridine **I**.

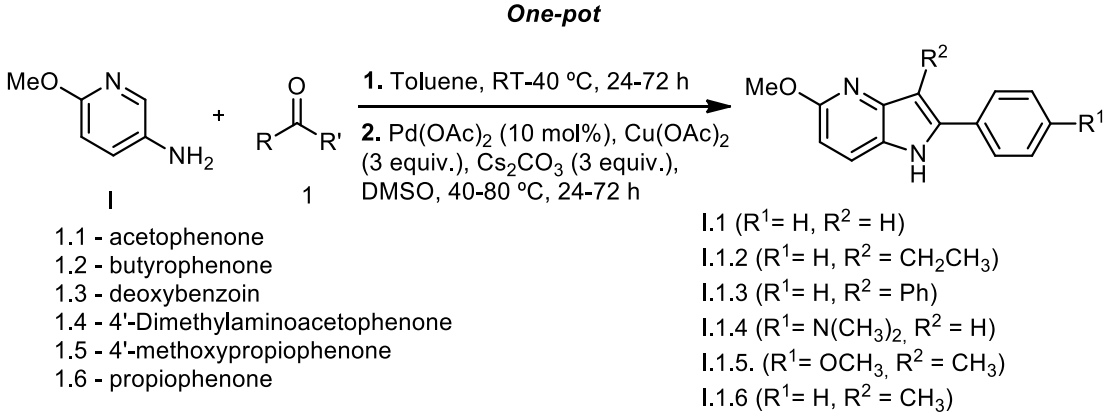
On the other hand, aminopyridine **IV** gave the lowest conversion (Table 5 – entry 2), with only 5% yield of the corresponding azaindole. This aminopyridine has a resonance effect from the amino group *para* to the nitrogen in the pyridine ring, resembling aminopyridine **II**. The low yield obtained could be justified through a strong catalyst poisoning during the C–N cross-coupling reaction, since it was performed with monodentate XPhos. Further optimization for this aminopyridine is required, particularly with XantPhos in the C–N cross-coupling reaction, to retrieve more data.

Another relevant observation is the regioselectivity of the reaction. Such as for aminopyridine **I**, for aminopyridine **III**, there can also be two isomers formed, depending where C−H activation takes place. Using silver salts in the reaction condition originates isomer **III.2** as the minor isomer and isomer **III.1** has the major product, *i.e.* there was an inversion of the regioselectivity of the reaction, since now the major product results from closing at position C-4 of the aminopyridine (affording 6-azaindole). The use of silver salt increasing the yield of the 6-aza isomer was already observed for aminopyridine **I** when silver was added to the catalytic system and the isomers yield was equal. This suggests that we can manipulate the regioselectivity of the reaction to obtain one or another isomer be changing the catalytic system.

2.3. Azaindole synthesis via ketone condensation/C−H activation reaction

The imine/enamine intermediates for azaindole synthesis can also be obtained through the condensation of ketones with aminopyridines, has published by authors such as Lachance[63]. Since vinyl bromides are commercially scarce and of difficult synthesis, we wanted to find another path to obtain the intermediate that would allow us a facile access to a variety of structures. Hence, we decided to try a ketone condensation/C−H activation reaction, similar to the C−N cross-coupling /C−H activation procedure developed.

Initially, we aimed to find the best substrate for the optimization of the reaction by observing which ketone would react better to the condensation or/and C−H activation with aminopyridine **I**. For this purpose, we searched various ketones under the C−H activation conditions optimized for aminopyridine **I** (Scheme 40). The condensation conditions applied were toluene heating between RT-40 ºC for 24-72 h until completion of the condensation reaction controlled by TLC. Unfortunately, only trace amount of azaindole was obtained for all the substrates tested.

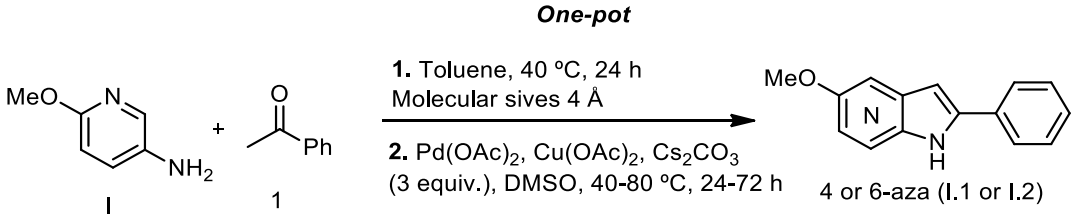


Scheme 40 – Search for the best ketone substrate for the ketone condensation/C−H activation reaction in the synthesis of azaindole structures.

Even though we obtained trace amount of azaindole for ketone **1.1** in the ketone search phase (Table 6 – entry 1). The conditions applied for the condensation reaction appeared to be appropriate, since through TLC analysis, the reaction was complete within 24 h at 40 ºC, in toluene. We decided to test other conditions for the subsequent C−H activation reaction between aminopyridine **I** and ketone **1.1** (Table 6), as these substrates originate the same intermediate as the C−N cross-coupling reaction developed.

However, while the condensation reaction was apparently complete through TLC analysis, the same C−H activation reaction conditions didn't afford similar yields of azaindole to the C−N cross-coupling/C-H activation approach. Thus, it was considered that the absence of the first catalytic system used for the C–N cross-coupling reaction might affect the reaction outcome, since this was the major difference between the two methods. Hence, we evaluated various amounts of the C−H activation catalytic system and its impact on the azaindole yield obtained, driven by the assumption that the C−N cross-coupling catalytic system was favoring, in some way, this step.

Table 6 – C−H activation conditions tested for the one-pot, ketone condensation/C−H activation reaction.



Entry	Pd cat. (mol%)	[Ox] (equiv.)	I.1 Yield (%)	I.2 Yield (%)
1	$Pd(OAc)_2$ (10)	$Cu(OAc)_2$ (3)	trace	trace
2	$Pd(OAc)_2$ (20)	$Cu(OAc)_2$ (3)	trace	trace
3	$Pd(OAc)_2$ (20)	$Cu(OAc)_2$ (6)	16	trace
4	$Pd(OAc)_2$ (15)	$Cu(OAc)_2$ (4)	21	trace

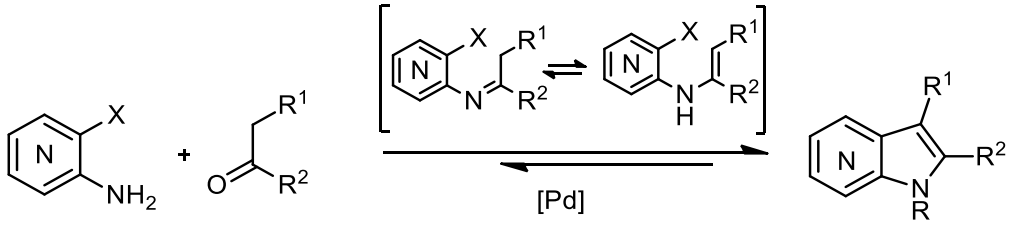
Since trace amounts and very low yields of azaindole were still being obtained, we conclude that the problem couldn't be the C−H activation reaction conditions. Still, we observed some interesting factors regarding the catalytic system amounts. While 10mol% of $Pd(OAc)_2$ and 3 equiv. of $Cu(OAc)_2$ only afforded trace amounts of azaindole, double the amount of these reagents increased the yield up to 16% of **I.1** (Table 6 – entry 3). In contrast to the latter result, a small decrease to 15mol% of $Pd(OAc)_2$ and 4 equiv. of $Cu(OAc)_2$ actually afforded a higher yield of 21% (Table 6 – entry 4). This could be justified by the fact that a large amount of copper, such as 6 equiv., negatively impacts the work-up of the reaction. With these quantities, a more restrictive celite pad filtration must be used to avoid most of the copper from transferring, and the extractions to remove the DMSO and some additional cooper from the mixture all translate into bigger losses of azaindole in the work-up and, subsequently, lower yields.

Lastly, we turned our attention to the condensation reaction and realized that a considerable amount of aminopyridine was recovered during the purification process. Hydrolysis wasn't a viable option since dry solvents and molecular sieves were being used during the condensation reaction. One possible explanation can lay on the fact that molecular sieves were retaining part of the aminopyridine, given that aminopyridines are basic in nature and molecular sieves are acidic.

Since the condensation reaction wasn't complete, the amount of precursor for the C−H activation step was a lot smaller than anticipated. Isolation of the intermediate from this reaction revealed a rough condensation yield of approximately 47%, (analysis by TLC, ^{1}H NMR couldn't be

performed). This means that less than half the expected quantity of imine was reacting in the C−H activation step. The yield of the C−H activation reaction would in fact be around 40% (For 15mol% of $Pd(OAc)_2$ and 4 equiv. of $Cu(OAc)_2$), if the reaction didn't proceed through a one-pot procedure. This is an interesting indication, suggesting that a one-pot procedure is not the best option to carry a ketone condensation/C−H activation reaction, and that a step-wise procedure might result in more satisfactory yield with the advantage of providing a wider reaction scope, *versus* the alkenyl bromides, through the usage of various ketones.

A relevant observation regarding aminopyridines and ketone condensation can also be made from Lachance work on azaindole synthesis through ketone condensation/Heck reaction[63]. Given the cascade profile of the reaction developed by the group, the equilibrium towards the formation of the intermediate is naturally shifted since the latter immediately reacts through Heck reaction to originate the azaindole (Scheme 41).



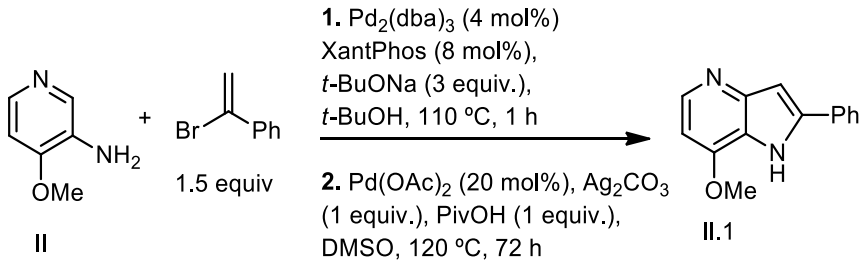
Scheme 41 − Cascade ketone condensation/Heck reaction from Lachance work.

In our case, the imine/enamine intermediate is synthesized completely before the C−H activation catalytic system is added, so there is no component that pushes the condensation reaction towards the intermediate formation. Hence another interesting alternative would be to perform the condensation reaction in the presence of the C−H activation catalytic system.

2.4. Investigation of the mechanism of the C−H activation/functionalization reaction

2.4.1. Studies on formation of imine/enamine intermediate

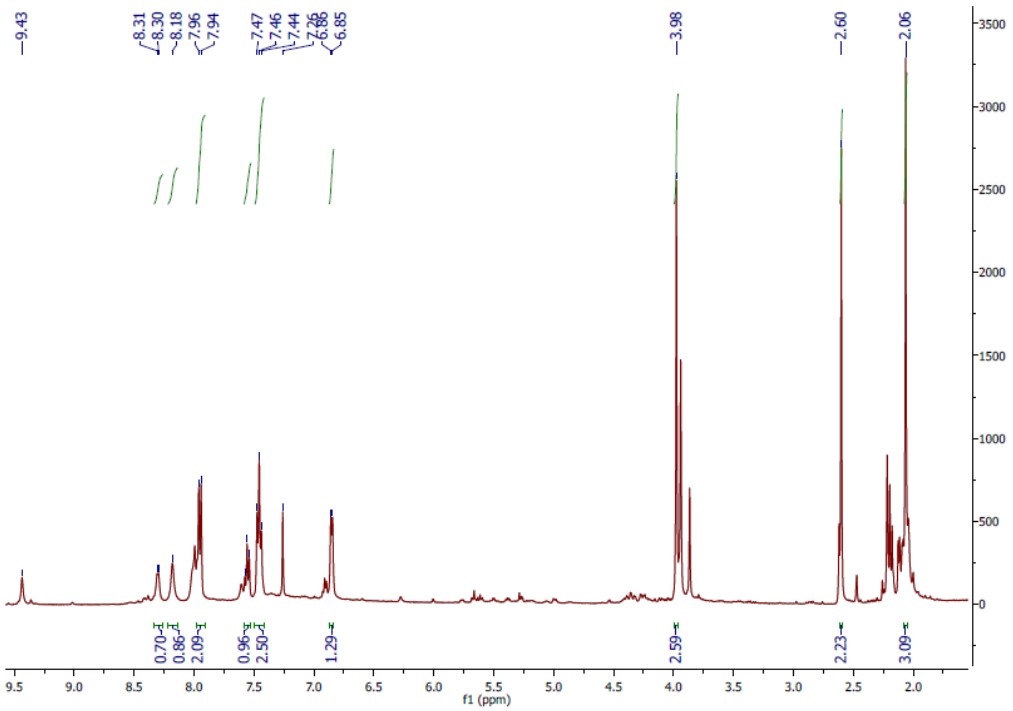
During isolation and purification through column chromatography of azaindole **II.1** (Scheme 42), the imine/enamine intermediate from the respective reaction was also isolated. In order to get some insight into this intermediate, ^1H NMR was performed (Scheme 43). Analysis of the spectrum and posterior NMR data pointed to a structure that is compatible with a complex adduct of the latter, that is in equilibrium with the imine intermediate.



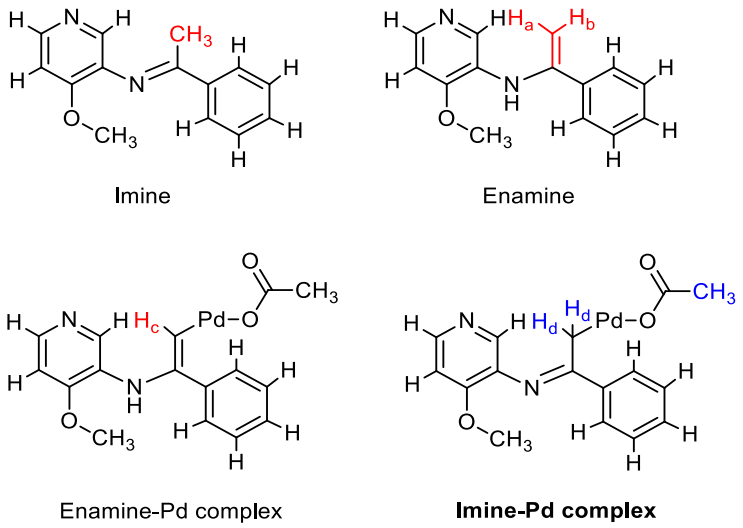
Scheme 42 – Reaction conditions from where the intermediate was isolated.

Firstly, it was observed that both aromatic systems from the aminopyridine and α-bromostyrene are present between the expected chemical shifts (8.31-6.85ppm), as well as the signals from protons of the methoxy group from the aminopyridine at 3.98ppm. Since there are no proton signals in the region assigned to double bond systems (4-5ppm) it is also safe to assume that the C−N cross-coupling reaction was successful, and we are not seeing a mixture of the two reagents, separately, in the spectrum. Additionally, the absence of signals from the olefinic protons (double bond system) also makes it unlikely to be the enamine intermediate, due to lack of the characteristic hydrogens signals associated with this structure (Scheme 44 − H_a and H_b).

The imine intermediate could be a possibility, since the signals and chemical shifts present in the ^{1}H NMR spectrum are compatible with the structure, particularly the singlet at 2.60ppm could correspond to the methyl protons from the imine (Scheme 44 – Imine). However, this singlet doesn't integrate to 3 protons, but, in fact, 2. Also, another singlet integrating for 3 protons at 2.06 ppm is present, but the chemical shift is not compatible with the protons in question.



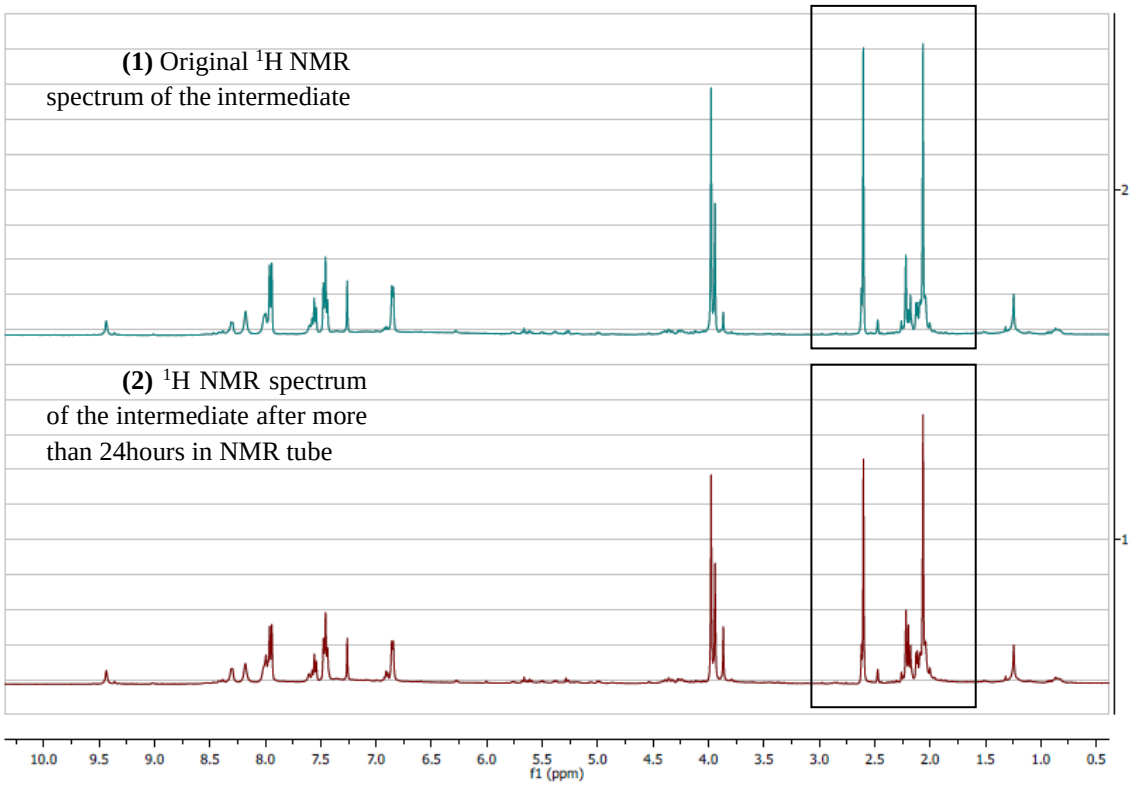
Scheme 43 – Original ^{1}H NMR spectrum of intermediate of azaindole **II.1** reaction, in $CDCl_3$, performed after preparation of the sample.



Scheme 44 – Possible structures for the intermediate of azaindole **II.1** reaction. Red indicates the ^{1}H NMR signals that are absent from the spectrum. Blue indicates the signals that lead to the structure proposed for the intermediate.

Given the reaction conditions, it was envisaged that the observed signals were due to the presence of the product of the enamine addition to the palladium catalyst, such as illustrated in Scheme 44 – Imine–Pd complex, with the 2.06 ppm singlet belonging to the CH_3 group from the acetate of palladium acetate. Another possibility could be the enamine addition directly to the acetate group, with no palladium metal present, but this would significantly move the chemical shift of H_d protons towards lower fields in the spectrum. However, all the chemical shifts predicted for the Imine–Pd complex are within the chemical shifts present in the spectrum.

Interestingly, a new ^1H NMR spectrum of the same sample performed after 24 hours later had a clear difference in the integration of the signal at 2.60 ppm, which suggested the presence of 3 protons. This would be compatible with the imine structure. It seemed that we were in the presence of an equilibrium in solution, where palladium acetate could be coordinated, or not, to the imine, since all the remaining spectrum maintained its original state except for this particular signal (Scheme 45).

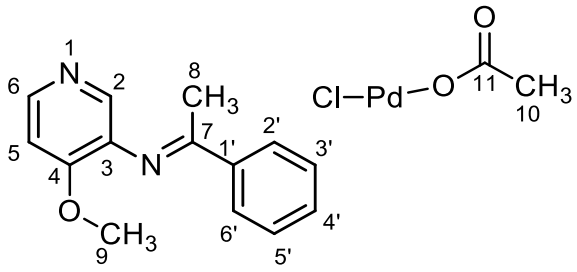


Scheme 45 – ^1H NMR spectrums of the imine intermediate in $CDCl_3$. (1) – After 24 h in the NMR tube. (2) – the original spectrum performed after NMR tube preparation. The distinct difference of integral signal is highlighted in the box.

The complete assignment and the proposed structure of the molecule is presented in Tables 7 and 8.

Although the spectrum was very complex and not pure, complete attribution pointed to the imine structure. It was confirmed through HSQC that the 2.60 ppm signal didn't correspond to a DMSO residual signal, since the chemical shift of the respective carbon was of 26,46 ppm, significantly different than reported (^{1}H NMR($CDCl_3$) DMSO residual signal: singlet, 2,62 ppm; ^{13}C NMR($CDCl_3$) DMSO residual signal: 40,76 ppm). In fact, through HMBC there is a correlation between protons at 2,60 ppm and a quaternary carbon that has been attributed to C1', making it even more clear that this signal is from proton C8–H.

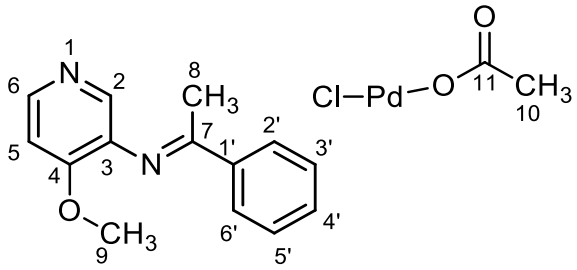
Table 7 – ^{1}H NMR attribution of the intermediate of azaindole **II.2** reaction, in $CDCl_3$, after 24 h in the NMR tube.



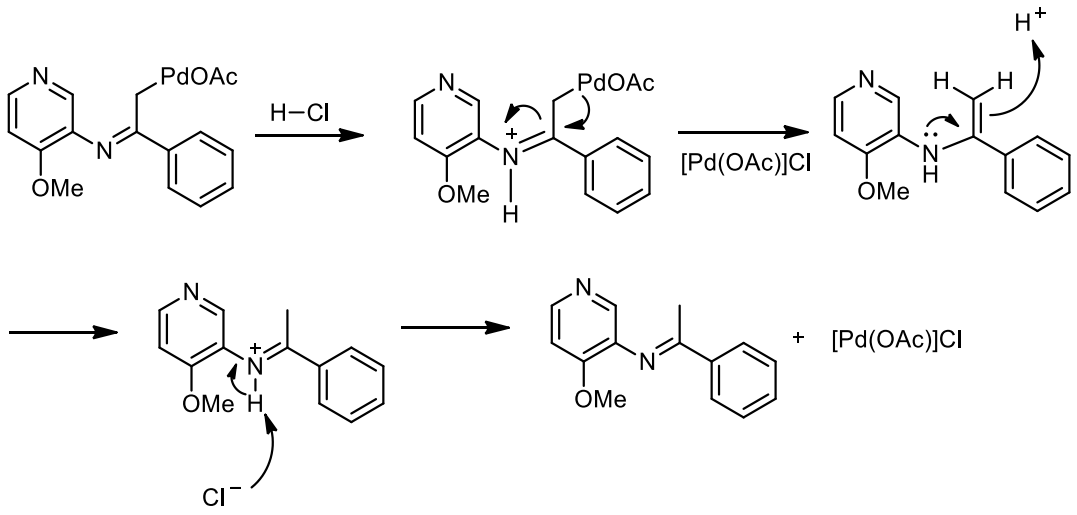
Chemical Shift (ppm)	Multiplicity	J (Hz)	Integration	COSY	Assignment
8,30	duplet	4,5	1H	6,86	C6–H
8,00	singlet	-	1H	6,86	C2–H
7,95	duplet	8,0	2H	7,46	C2'–H; C6'–H
7,56	triplet	7,2	1H	7,46	C4'–H
7,46	triplet	7,4	2H	7,56, 7,95	C3'–H; C5'–H
6,86	duplet	5,2	1H	8,30; 8,00	C5–H
3,98	singlet	-	3H	-	C9–H
2,60	singlet	-	3H	-	C8–H
2,06	singlet	-	3H	-	C10–H

The signals from the acetate are in complete agreement with the predicted chemical shifts for this group hence, its existence, is extremely likely. The only possible source of acetate would be the palladium catalyst and, since there are no visible NMR correlations within the molecule to this group, we presume it to be coordinated with palladium, since the metal would interfere with possible correlations. As $CDCl_3$ often produces hydrochloric acid, the mechanism of dissociation of the metal to form the imine could be as the one proposed in Scheme 46.

Table 8 – ^{13}C NMR attribution of the intermediate of azaindole **II.2** reaction in $CDCl_3$ after 24 h in the NMR tube.

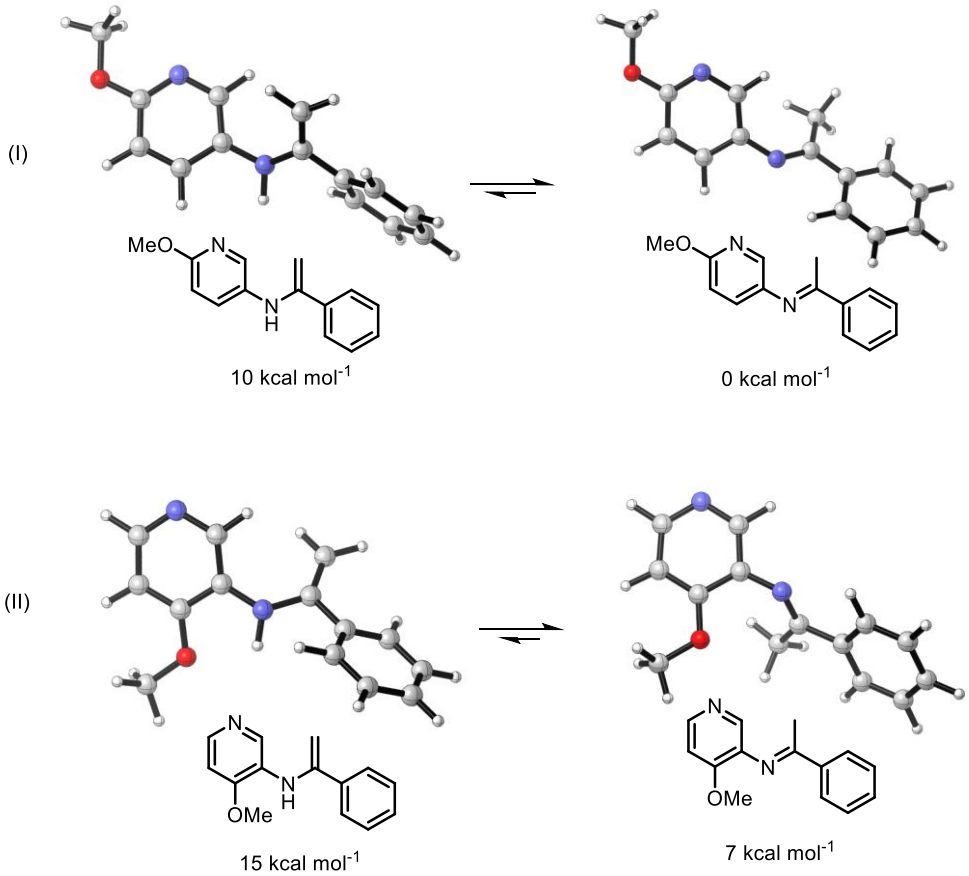


Chemical Shift (ppm)	HSQC	HMBC	Assignment
198,21	-	2,60; 7,95	C7
174,78	-	2,06	C11
155,19	-	3,98; 6,86	C4
145,22	8,30	-	C6
137,08	-	7,46; 2,60	C1’
136,22	8,00	-	C2
134,95	-	6,85	C3
133,09	7,56	7,95	C4’
128,54	7,95	7,56; 7,46	C2’; C6’
128,27	7,46	7,56; 7,46	C3’; C5’
105,90	6,86	-	C5
56,06	3,98	-	C9
26,58	2,60	-	C8
21,22	2,06	-	C10



Scheme 46 − Mechanism proposed for the dissociation of the palladium acetate from the imine intermediate in the NMR tube with $CDCl_3$.

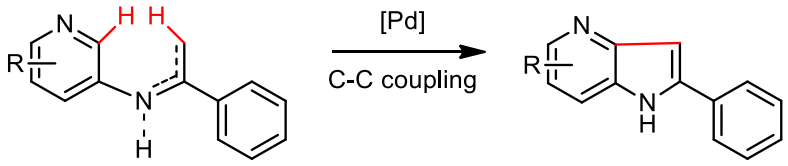
Additionally, computational data has revealed the imine tautomer to be electronically more stable than the enamine (Scheme 47), at room temperature, justifying the enamine conversion into the imine after the dissociation process.



Scheme 47 – Relative free-energies for the low-energy conformers of the imines/enamines of the reaction of aminopyridines **I** and **II**.

2.4.2. Plausible proposal of the mechanism

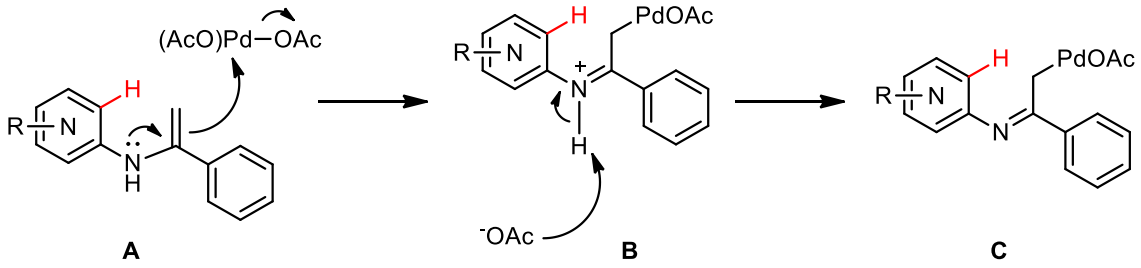
The reaction that originates the azaindole structure from the imine/enamine intermediate is an intramolecular CDC type reaction, since two C−H bonds are being coupled (Scheme 48). Although throughout this thesis it has been referred to the C−H reaction as an activation reaction, the palladium(II) catalyst, can interact with these bonds either through activation or functionalization reaction, depending on if there is an actual organometallic compound being formed or just an ionic interaction between the molecule and the metal (See 1.4.1.), respectively.



Scheme 48 − Azaindole formation via intramolecular C−C cross-coupling reaction of imine/enamine intermediate.

Pd(II) is an electron poor, late transition metal in an already high oxidation state, so it is most likely to react via electrophilic activation mechanisms.[46,70] If the enamine tautomer is the starting substrate, the reaction mechanism could be a tandem C(sp^2) −H/ C(sp^2) −H activation, starting with C−H activation at the C(sp^2) −H hydrogen, via electrophilic substitution, with acetic acid release originating (Scheme 49).

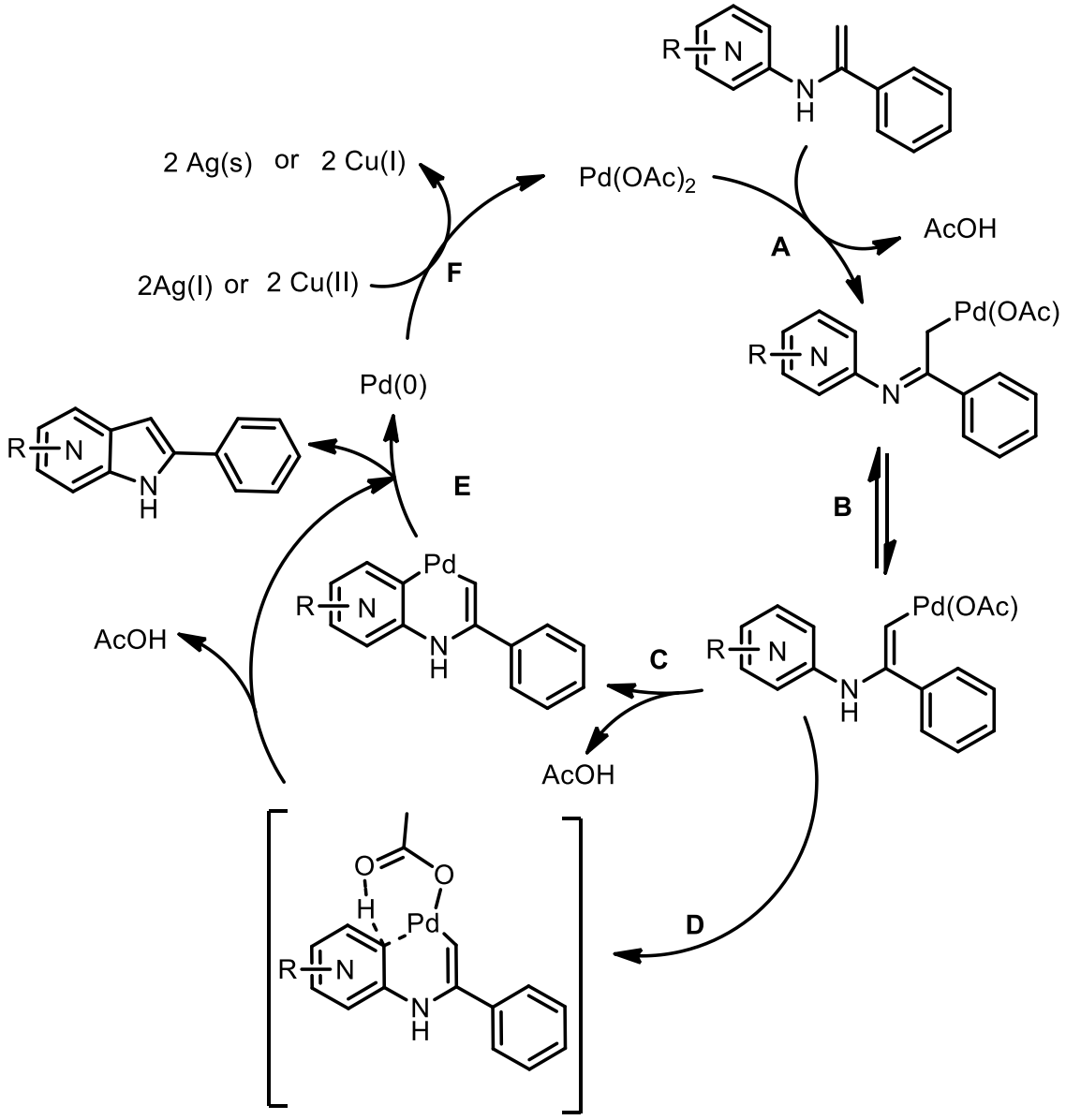
In the case we have the imine intermediate reacting firstly, the palladium(II) catalyst would have to undergo C−H activation at an C(sp^3) −H hydrogen, which is more difficult to occur due to the fact that this type of C−H bond is the least acidic. Also, the metal has a steric hindrance effect regarding its addition to the C(sp^3) −H bond, because of the geometry of the orbitals, even though it is possible to occur, as various authors reported C(sp^3) −H activation[47] an even tandem C(sp^2) −H/C(sp^3)−H activation for intramolecular cyclization purposes.[71] Nonetheless, the first case would be in accordance with the intermediate that we propose to have isolated (Scheme 49 – C) (See 2.4.1). Also, the computational data (Scheme 47) only indicates that, at room temperature, the imine is the most stable tautomer, but at 120 ºC applied in the reaction conditions, this prediction is no longer valid.



Scheme 49 − C−H activation at the C(sp^2) –H hydrogen of the enamine, via electrophilic substitution.

Species C now must interact with another C(sp^2) −H bond to cyclize into the azaindole. However, the geometry of the carbons to be coupled is conflicting, since now the first carbon is in a sp^3 hybridization. Since this palladium complex resembles an imine substrate, it is possible that tautomerization occurs before another C−H interaction, so that the resulting cycle has a stable geometry. However, we can't confirm if this reaction is C−H activation since no intermediate from this step was isolated.

With all these factors in mind, we proposed the mechanism illustrated in Scheme 50, as it follows the most logic reactivity for these substrates. In step **A** there is C−H activation at the C(sp^2) −H bond via an electrophilic substitution. The resulting species engages in a tautomerism alike equilibrium (**B**) mediated by the base used in the reaction and the acetic acid released. Subsequently, follows C−H activation (**C**) to originate the palladacycle or functionalization (**D**). Reductive elimination originates the azaindole nucleus and palladium(0) which is re-oxidized to palladium(II) by an external oxidant. Mass spectrometry experiments are being carried, as well as DFT calculations, to support a plausible mechanism.

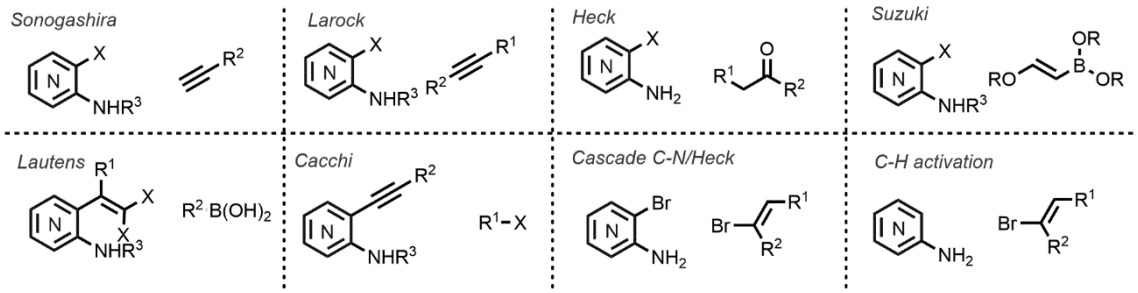


Scheme 50 Reaction mechanism proposed for the C−H activation reaction in the synthesis of azaindoles.

Chapter 3 – Final Remarks and Future Perspectives

3.1. Final Remarks

Many of the known synthetic strategies to obtain azaindoles come from halogenated substrates (Scheme 51, X = Cl, Br or I). However, this pre-functionalization of the substrate costs time, resources and is often poor in regioselectivity. The C−H activation reaction is an emerging solution to this type of problem, as it avoids the need of a functional group in the substrate to perform a reaction and, instead, attempts to directly interact with a C−H bond, which was often regarded as unreactive.



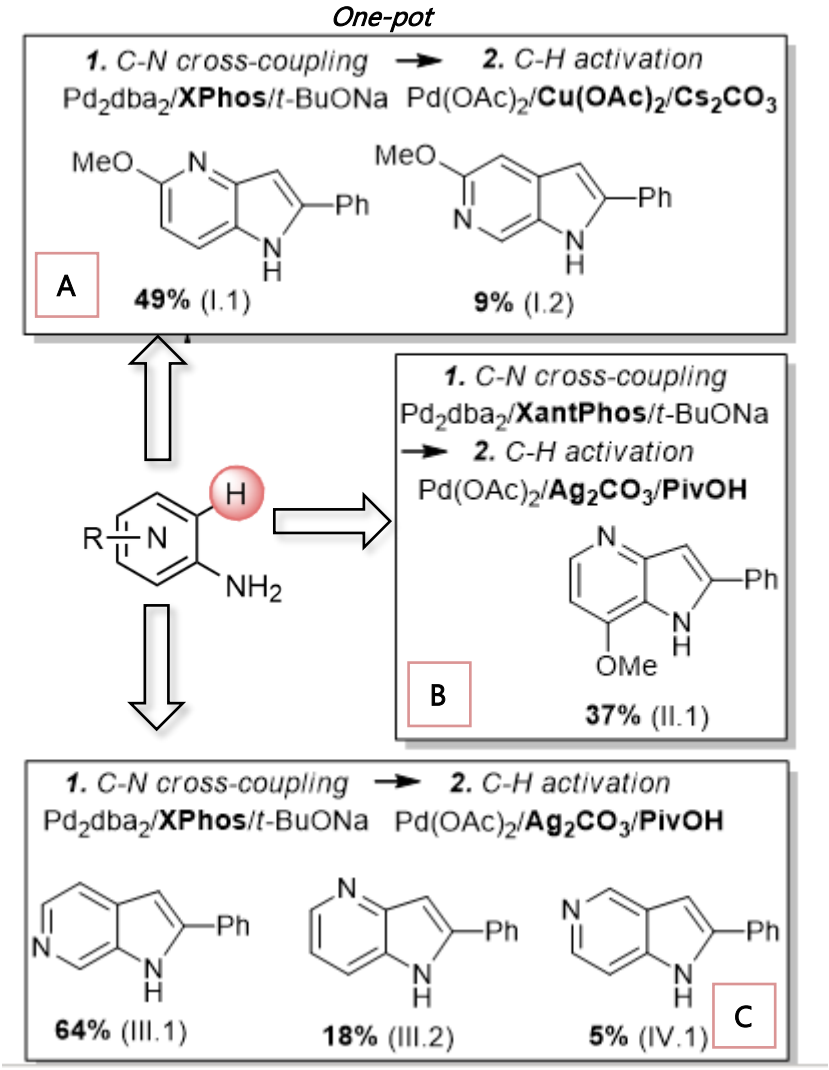
Scheme 51 − Synthetic methods developed for the synthesis of azaindoles.

Concerning the synthesis of azaindole substrates using C−H activation reactions, up to date, only two examples can be found in the literature, which are restricted to one isomer (7-azaindole).

In order to develop a methodology to attain the azaindole core through C−H activation mechanism, it was envisioned the formation of a primary intermediate, an imine/enamine, through reaction with an alkenyl bromide, and subsequent intramolecular C−H activation to cyclize into the azaindole.

Our previous knowledge of C−N cross-coupling reactions of aminopyridines, allowed us to access the imine/enamine intermediate from non-halogenated aminopyridines. The reaction was first optimized for 5-amino-2-methoxypyridine (aminopyridine **I**) and *α*-bromostyrene, which resulted in yields of 49 and 9% for azaindoles **I.1** and **II.2**, respectively (total conversion of 58%) – Scheme 52 – **A**. The catalytic system chosen for the C−N cross-coupling was Pd_2dba_3/XPhos/*t*-BuONa and for the C−H activation reaction was $Pd(OAc)_2/Cu(OAc)_2/Cs_2CO_3$. The regioselectivity of the reaction for this substrate under these conditions is towards the formation of the 4-azaindole (**I.1**), presumably due to the polarization of the C−H bond adjacent to the nitrogen in the pyridine ring, making this bond more subjected to catalyst insertion. However, during the optimization process it was discovered that the use of silver salts (Ag_2CO_3) influenced the outcome of the reaction. Silver salts coordinate with the nitrogen from the pyridine ring reducing its basicity. Hence, the electronegative effect from the nitrogen atom is reduced and the two C−H bonds became equally liable of C-H activation (16% yield for both **I.1** and **I.2**).

Moving on to another activated substrate, 3-amino-4-methoxypyridine (aminopyridine **II**) – Scheme 52 – **B** – we found that the position of the methoxy group in the ring had a huge impact on the reactivity of the aminopyridine. The presence of this group at the *para* position made aminopyridine **II** much more prone to poison the catalyst due to a strong coordination of the nitrogen in the pyridine ring to the metal, a result from both resonance and steric effects. To avoid this issue, both a bidentate phosphine ligand – XantPhos – and silver salts were used in the C−N cross-coupling/C−H activation reactions, respectively. The combination of the bulkiness of the ligand and the reduced basicity from silver coordination allowed to obtain azaindole **II.1** in 37% yield.



Scheme 52 − Azaindoles synthesized in this master thesis and respective catalytic systems used.

Experiments with microwave irradiation demonstrated that the C–N cross-coupling reaction was much more efficient under these conditions, given access to the imine/enamine intermediates from aminopyridines I and II within 15 min of MW 110 ºC, instead of 1-2 h of thermal heating.

Additionally, it was possible to apply these same conditions and successfully obtain the intermediates for 3-aminopyridine (aminopyridine **III**) and 4-aminopyridine (aminopyridine **IV**), which did not provide results under thermal heating conditions. Hence, the respective azaindole from each unsubstituted aminopyridine was synthesized under the conditions of Pd_2dba_3/XPhos/*t*-BuONa and $Pd(OAc)_2/Ag_2CO_3$/PivOH – Scheme 52 – **C**.

Aminopyridine **III** afforded the highest conversion (64% of **III.1** and 18% of **III.2** yield) indicating that the absence of the methoxy group was beneficial for the C–H activation. This is possibly since the pyridine ring is, without the electron-donating group, much more electron-deficient and subsequently, the C–H bond less stable and more susceptible to activation. Azaindole **IV.1** had the lowest yield observed (5%). This is probably due to a similar effect to aminopyridine **II**, since the amine group in *para* position must exert significant electron-donating effect that raises basicity of the nitrogen in the pyridine ring, hence catalyst poisoning. Since only XPhos was used, the low yield might be justified.

Additionally, another method to attain the imine/enamine intermediate was tested. The condensation of aminopyridine **I** with various ketones afforded the respective azaindoles but only in trace amounts. We concluded that the condensation under the conditions applied is not efficient for a one-pot ketone condensation/C−H activation procedure.

An intermediate was also isolated, which NMR data points to be the product of addition of the enamine intermediate to the palladium acetate catalyst. NMR data from the same sample hours later resembled a dissociation, in solution, from the metal catalyst to the imine, via enamine, in accordance with the fact that the imine product is the more electronically stable, as shown by computational calculations. The isolated adduct shed some light regarding the reaction mechanism, since an organometallic compound is being formed, the reaction proceeds, firstly, through an actual activation of the $C(sp^2)$–H bond, and not functionalization.

To conclude, this master thesis has contributed to the development of an innovative protocol that combines a C−N cross-coupling/C−H activation reaction catalyzed by palladium, of simple aminopyridines and *α*-bromostryrene, in a one-pot procedure. The method enabled to attain 4- and 6-azaindole isomers, in a total of six azaindole structures, three of them completely new (**I.1**, **I.2** and **II.1**). Additionally, this thesis offers a rare insight into the reactivity of each aminopyridine as well as the manipulation of the catalytic system in the reaction outcome. Preliminary studies towards a more precise reaction mechanism for the C–H activation were also performed.

3.2. Future Perspectives

The future work of this project has three main objectives:

- Expanding the scope of the C−N cross-coupling/C−H activation reaction to other alkenyl bromides, which will be performed with 3-aminopyridine, with the aid of microwave irradiation in the C−N cross-coupling step. This should also involve experimenting with the $Pd(OAc)_2/Cu(OAc)_2/Cs_2CO_3$ catalytic system to observe the inversion of regioselectivity and allow the facile route towards either 4- or 6-azaindole isomers.

- Explore a stepwise reaction instead of a one-pot procedure in both C−N cross-coupling/C−H activation and ketone condensation/ C−H activation reactions. This will most likely raise the yields of the reaction and, if applied to the latter procedure, access a variety of structures from ketones that are not attained using vinyl bromides.

- DFT, MS and further NMR investigation of the reaction, to ascertain if it is a dual activating mechanism taking place and understand how to manipulate the conditions to favor the reaction outcome.

Additionally, this new C−H activation of aminopyridines can offer a route towards functionalization of similar substrates, and even azaindoles itself.

Chapter 4 – Experimental

4.1. General Information

The experimental part of this work involved the use of general laboratory procedures. All reagents and solvents were acquired commercially and used without further purification, unless otherwise mentioned. All mentioned solvents were, when necessary, dried using typical methods[72,73], i.e. distillation under drying agents or usage of activated molecular sieves. Activation of the molecular sieves was performed by heating at 300 °C in a muffle furnace for 3h or by heating in a microwave for 10 minutes.

Analytical TLC was performed on Merck Kieselgel GF 254 0.2 mm plates supported on aluminum. Preparative TLC was performed using Merk Kieselgel 60GS254 silica gel for TLC supported on a glass surface with the described eluent for each case. Column chromatography was performed using Merck Kieselgel 60A silica gel (70-200 mesh) and the described eluent for each case.

ATR-FTIR spectrums were acquired using a Perkin-Elmer Spectrum Two spectrophotometer. Transmittance of the sample was acquired on between 4000 and 600 cm^{-1}.

NMR spectrum were acquired with Bruker ARX 400 or Bruker Avance III 400 spectrometers. ^{1}H-NMR and ^{13}C-NMR spectrum were measured at 400 and 101 MHz, respectively. The samples were prepared on 5 or 3 mm NMR tubes using $CDCl_3$, DMSO-d_6 or acetone-d_6, as solvents and the corresponding trace as reference signals. The NMR signals are described with chemical shift (δ, in ppm), source of signal (R–H) and relative intensity of signal multiplicity (nH, with n being the number of protons). NMR signals are described as singlet (s), doublet (d), triplet (t) and multiplet (m) with coupling constant (J) being given in Hz.

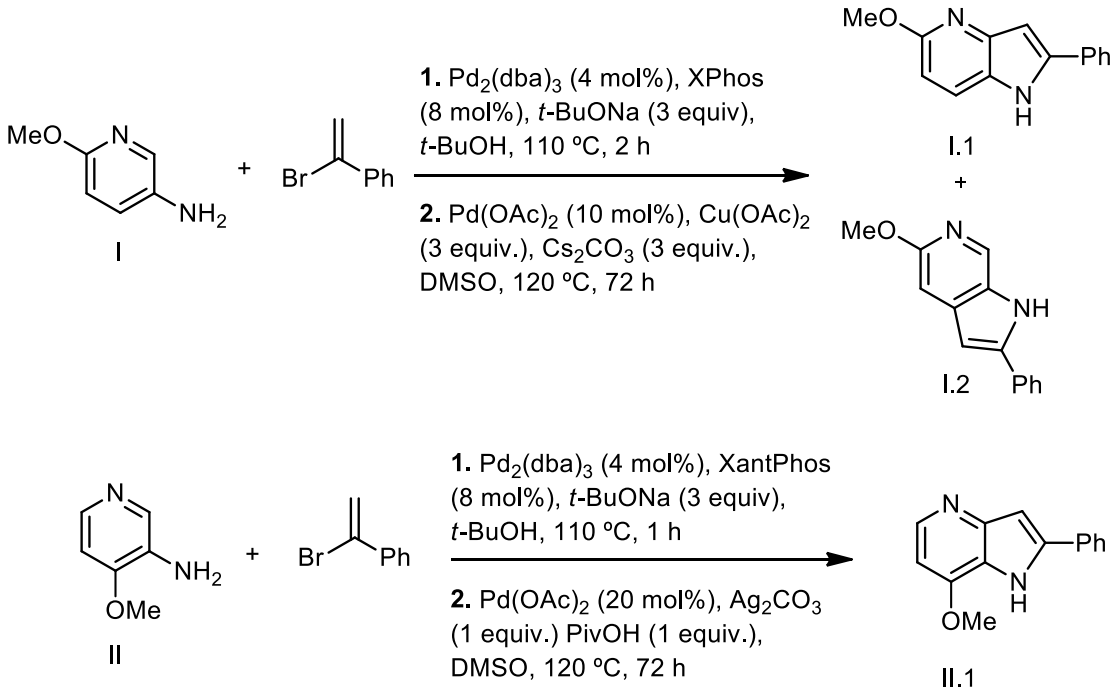
4.2. Azaindole synthesis via C–N cross-coupling/C–H activation

4.2.1. General procedure for the one-pot C–N cross-coupling/C–H activation reaction

A sealed tube equipped with a magnetic stirring bar was charged with $Pd_2(dba)_3$ (4mol%), ligand (8mol%), *t*-BuONa (3 equiv.), and substrate **I** or **II** (1 equiv., 30 mg). The tube was sealed with a suba-seal and evacuated/filled with nitrogen three times. Dried *t*-BuOH (0.1M) was added, followed by *α*- bromostyrene (1.5 equiv.), and the reaction was stirred at 110ºC until completion under TLC control (1-2 h).

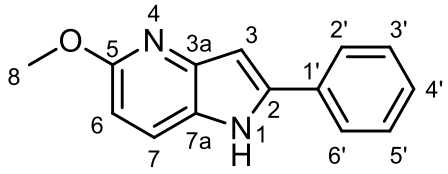
After completion of the reaction monitored by TLC, the solvent was evaporated to dryness and a catalytic system consisting of $Pd(OAc)_2$/Oxidant/Additive or Base were added to the sealed tube, which was again evacuated/filled with nitrogen three times. Dried DMSO (0,1M) was added, and the reaction was stirred for 72 h at 120 ºC.

The solution was cooled to room temperature, filtered over a celite pad, washed with ethyl acetate and concentrated on the rotary evaporator. Extractions using ethyl acetate and brine were performed with the aqueous layer being extracted several times (at least 3). Combined organic layers were dried with Na_2SO_4, filtered and concentrated. The resulting oil was purified by column chromatography and preparative thin-layer chromatography to afford azaindoles **I.1**, **I.2** and **II.1**.



Scheme 53 – Optimized conditions for the synthesis of azaindoles **I.1**, **I.2** and **II.1**.

4.2.2. 5-methoxy-2-phenyl-1*H*-pyrrolo[3,2-*b*]pyridine (I.1)



The product was obtained as a brown oil (26.5 mg, 49%) after purification through column chromatography on silica-gel, hexane/ethyl acetate, with gradient.

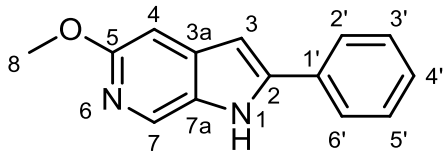
ATR-FTIR ν_{max} (cm^{-1}): 3674, 2973, 2905, 1582, 1410, 1223, 1261, 1060, 1074, 1050, 739.

^{1}H-NMR (400 MHz, $CDCl_3$) δ (ppm): 8.60 (s, N(1)–H, 1H), 7.66 (d, C6'–H, C2'–H, J = 7.2 Hz, 2H), 7.61 (d, C7–H , J = 8.4 Hz, 1H), 7.44 (t, C3'–H, C5'–H, J = 7.4 Hz, 2H), 7.33 (t, C4'–H, J = 7.2, 1H), 6.89 (s, C3–H, 1H), 6.60 (d, C6–H , J = 8.4, 1H), 4,01 (s, C8–H, 3H).

^{13}C-NMR (101 MHz, $CDCl_3$) δ(ppm): 160.29 (C5), 143.49 (C3a), 140.26 (C2), 131.92 (C1') 129.08 (C3', C5'), 128.16 (C4'), 125,76 (C7a), 125.15 (C2', C6'), 121.92 (C7), 105.63 (C6), 99.73 (C3), 53.54 (C8).

Mass spectrometry has been submitted - waiting for results.

4.2.3. 5-methoxy-2-phenyl-1*H*-pyrrolo[2,3-*c*]pyridine (I.2)



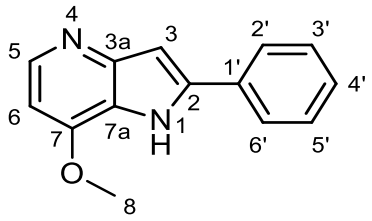
The product was obtained as a brown oil (4,9 mg, 9%) after purification through column chromatography on silica-gel, hexane/ethyl acetate, with gradient.

ATR-FTIR ν_{max} (cm^{-1}): 2925, 2852, 1741, 1626, 1468, 1232, 1144, 1038, 765, 697.

^{1}H-NMR (400 MHz, $CDCl_3$) δ (ppm): 8.41 (s, N(1)–H, 1H), 7.70 (d, C2'–H, C6'–H, J = 7.6, 2H), 7.48 (t, C3'–H, C5'–H, J = 7.6, 2H), 7.40 (t, C4'–H, J = 7.4, 1H), *6.99 (s, 1H), *6.90 (s, 1H), *6.70 (s, 1H).

^{13}C NMR and complete attribution couldn't be performed for this molecule due to the low amount obtained. *Signals can't be unequivocally be assigned. Further characterization is under development (Full NMR attribution and mass spectrometry)

4.2.4. 7-methoxy-2-phenyl-1*H*-pyrrolo[3,2-*b*]pyridine (II.1)



The product was obtained as a brown oil (20.0 mg, 37%) after purification through column chromatography on neutral alumina, hexane/ethyl acetate, with gradient.

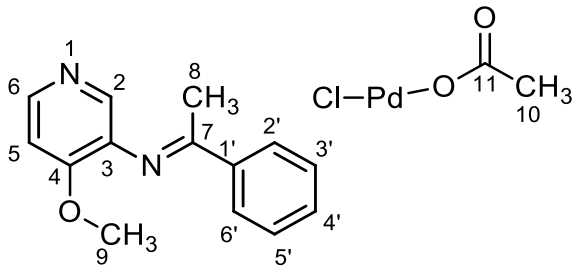
ATR-FTIR ν_{max} (cm^{-1}): 3371, 2972, 2924, 2859, 1629, 1563, 1456, 1414, 1301, 1116, 1093, 1049, 748, 696.

^{1}H-NMR (400 MHz, $CDCl_3$) δ (ppm): 8.28 (s, (N1)–H, 1H), 7.73 (d, C2'–H, C6–H', J = 7.5, 2H), 7.42 (m, C3'–H, C5'–H, C4'–H, J = 7.3 Hz, 3H), 7.35 (d, J = 7.1 Hz, 1H), 6.94 (s, C3–H, 1H), 6.58 (d, C6–H, J = 5.0 Hz, 1H), 3.97 (s, C8–H, 3H).

^{13}C-NMR (101 MHz, $CDCl_3$) δ(ppm): 152.37 (C7), 147.00 (C3a), 140.86 (C2), 131.45 (C1'), 129.35 – 129.20 (C3', C6', C4'), 128.52 (C5), 125.59 (C2', C6'), 120.86 (C7a), 99.79 (C3), 98.88 (C6), 55.55 (C8).

Mass spectrometry has been submitted - waiting for results.

4.2.5. (*E*)-4-methoxy-*N*-(1-phenylethylidene)pyridin-3-amine and palladium acetate chloride salt (II.2)



This is a proposed structure given the data yet available. Further characterization in under development.

^{1}H-NMR (400 MHz, $CDCl_3$) δ (ppm): 8.30 (d, C6–H, J = 4.5 Hz, 1H), 8.00 (s, C2–H, 1H), 7.95 (d, C2'–H, C6'–H, J = 8.0 Hz, 2H), 7.56 (t, C4'–H, J = 7.2 Hz, 1H), 7.46 (t, C3'–H, C5'–H, J = 7.4 Hz, 2H), 6.86 (d, C5–H, J = 5.2 Hz, 1H), 3.98 (s, C9–H, 3H), 2.60 (s, C8–H, 3H), 2.06 (s, C10–H, 3H).

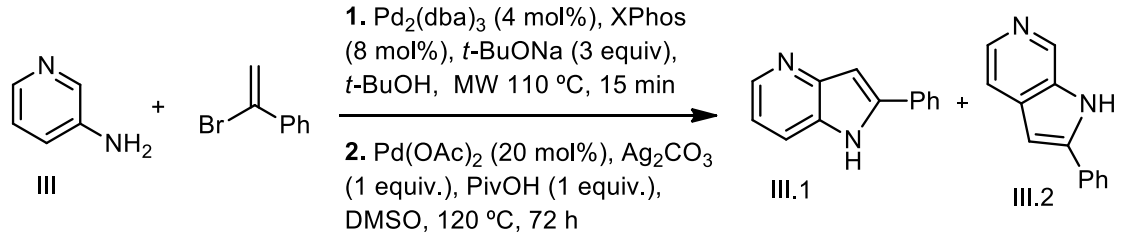
^{13}C-NMR (101 MHz, $CDCl_3$) δ(ppm): 198.21 (C7), 174.78 (C11), 155.19 (C4), 145.22 (C6), 137.08 (C1'), 136.22 (C2), 134.95 (C3), 133.09 (C4'), 128.54 (C2'; C6'), 128.27 (C3';C5'), 105.90 (C5), 56.06 (C9), 26.58 (C8), 21.22 (C10).

4.2.6. General procedure for the C–N cross-coupling/C–H activation reaction of aminopyridine III under microwave conditions

A wide-neck vial for microwave heating was equipped with a magnetic stirring bar and charged with $Pd_2(dba)_3$ (4mol%), XPhos (8mol%), *t*-BuONa (3 equiv.), and substrate **III** (2 equiv., 30mg). The vial was closed with a stopper and evacuated/filled with nitrogen three times. 5 mL of *t*-BuOH were added, followed by *α*-bromostyrene (1 equiv.) and the reaction was stirred at MW 110ºC for 15 min.

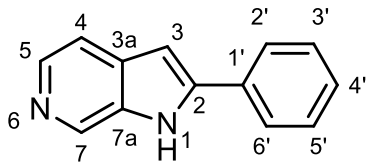
The mixture was transferred to a sealed tube, the solvent was evaporated to dryness and $Pd(OAc)_2$ (20 mol%), Ag_2CO_3 (1 equiv.), and PivOH (1 equiv.) were added to the sealed tube, which was evacuated/filled with nitrogen three times. Dried DMSO (0,1M) was added, and the reaction was stirred for 72h at 120ºC under an oil bath.

The solution was cooled to room temperature, filtered over a celite pad, washed with ethyl acetate and concentrated on the rotary evaporator. Extractions using ethyl acetate and brine were performed with the aqueous layer being extracted several times (at least 3). Combined organic layers were dried with Na_2SO_4, filtered and concentrated. The resulting oil was purified by column chromatography to afford the azaindoles **III.1** and **III.2**.



Scheme 54 – Optimized conditions for the synthesis of azaindoles **III.1** and **III.2**.

4.2.7. 2-phenyl-1*H*-pyrrolo[2,3-*c*]pyridine (III.1)

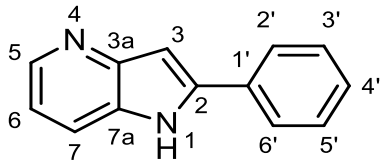


The product was obtained as a brown solid (19.2 mg, 64%) after purification through column chromatography on silica-gel, hexane/ethyl acetate, with gradient.

^{1}H-NMR (400 MHz, acetone-d6 + DBU) δ (ppm): 8.75 (s, C7–H, 1H), 8.08 (d, C5–H, J = 5.3 Hz, 1H), 8.00 (d, C2'–H, C6'–H, J = 7.3 Hz, 2H), 7.47 – 7.45 (m, C3'–H, C5'–H, C4–H, 3H), 7.36 (t, H12, 3H*), 6.90 (s, C3–H, 1H)

The NMR spectrum needs to be made in DMSO with DBU due to protonation of the substrate, from silica, during the purification process. Since these conditions weren't applied, the quality of the spectrum is very low. Comparison of the substrate with a sample previously synthesized in our group[27] were used to ensure compatibility through TLC while further NMR characterization was not performed.

4.2.8. 2-phenyl-1*H*-pyrrolo[3,2-*b*]pyridine (III.2)



The product was obtained as a brown solid (5,62 mg, 18%) after purification through column chromatography on silica-gel, hexane/ethyl acetate, with gradient.

^{1}H-NMR (400 MHz, DMSO-d6) δ (ppm): 11.79 (s, N(1)–H, 1H), 8.31 (d, C5–H, J = 3.5 Hz, 1H), 7.93 (d, C2'–H, C6'–H, J = 7.4 Hz, 2H), 7.76 (d, C7–H, J = 8.0 Hz, 1H), 7.50 (t, C3'–H, C5'–H, J = 7.6 Hz, 2H), 7.39 (t, J = 7.3 Hz, C4'–H, 1H), 7.08 (m, C6–H, 1H), 7.06 (s, C3–H, 1H).

This compound has been previously described in the literature.[27]

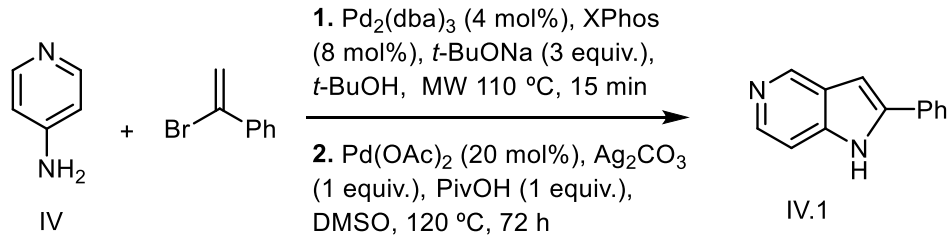
4.2.9. Procedure for the microwave aided C–N cross-coupling/C–H activation reaction of aminopyridine IV

A wide-neck vial for microwave heating was equipped with a magnetic stirring bar and charged with $Pd_2(dba)_3$ (4mol%), XPhos (8mol%), *t*-BuONa (3 equiv.), and substrate **IV** (1 equiv., 30 mg). The vial was closed with a stopper and evacuated/filled with nitrogen three times. 5 mL of *t*-BuOH were added, followed by *α*-bromostyrene (1.5 equiv.) and the reaction was stirred at MW 110 ºC for 15 min.

The mixture was transferred to a sealed tube, the solvent was evaporated to dryness and $Pd(OAc)_2$ (20 mol%), Ag_2CO_3 (1 equiv.), and PivOH (1 equiv.) were added to the sealed tube, which was evacuated/filled with nitrogen three times. Dried DMSO (0,1M) was added, and the reaction was stirred for 72 h at 120 ºC under an oil bath.

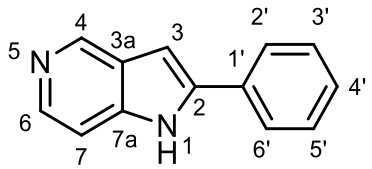
The solution was cooled to room temperature, filtered over a celite pad, washed with ethyl acetate and concentrated on the rotary evaporator. Extractions using ethyl acetate and brine were performed with the aqueous layer being extracted several times (at least 3).

Combined organic layers were dried with Na_2SO_4, filtered and concentrated. The resulting oil was purified by column chromatography to afford the azaindole **IV.1**.



Scheme 55 – Optimized conditions for the synthesis of azaindole **IV.1**.

4.2.10. 2-phenyl-1*H*-pyrrolo[3,2-*c*]pyridine (IV.1)



The product was obtained as an orange solid (2,85 mg, 5%) after purification through column chromatography on neutral alumina, hexane/ethyl acetate, with gradient.

^{1}H-NMR (400 MHz, DMSO) δ (ppm): 11.97 (s, N(1)–H, 1H), 8.82 (s, C4–H, 1H), 8.17 (d, J = 4.3 Hz, C6–H, 1H), 7.90 (d, J = 7.3 Hz, C2'–H, C6'–H, 2H), 7.49 (t, J = 7.7 Hz, C3'–H, C5'–H, 2H), 7.38–7.36 (m, C4'–H, C7–H, 2H), 7.04 (s, C3–H, 1H)

This compound has been previously described in the literature.[27]

4.3. Azaindole synthesis via ketone condensation

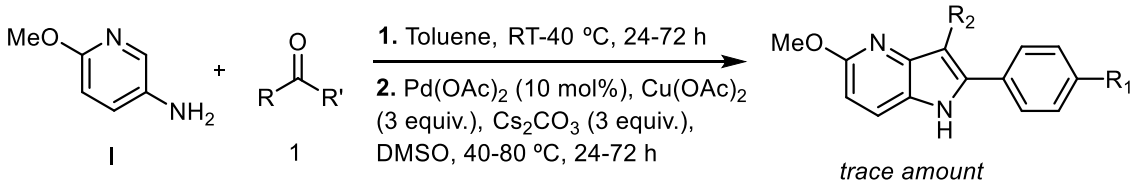
4.3.1. General procedure for the azaindole synthesis via ketone condensation

To a sealed tube equipped with a magnetic stirrer, it was added aminopyridine **I** (1 equiv., 30 mg), ketone (1.3 equiv.) and molecular sieves 3Å. The sealed tube was evacuated and refilled with N_2 three times and dried toluene (0,12M) was added. The reaction mixture was stirred between 24-48 h and room temperature to 40 ºC until completion observed through TCL and then evaporated to dryness before addition of $Pd(OAc)_2$ (10 mol%), $Cu(OAc)_2$ (3 equiv.) and Cs_2CO_3 (3 equiv.). The tube was evacuated/filled with nitrogen three times and dried DMSO (0,1M) was added.

The reaction mixture was stirred again at 40-80ºC for 24-72 h until completion was observed in TLC. The solution was allowed to cool to room temperature, filtered over a celite pad and concentrated on the rotary evaporator.

Extractions using ethyl acetate and brine were performed and the aqueous layer was extracted several times (at least 3). Combined organic layers were dried with Na_2SO_4, filtered and concentrated.

The resulting oil was purified by column chromatography and preparative thin-layer chromatography. All substrates synthesized were obtained in trace amount. Identification of the substrates was performed visually through TLC analysis due to the strong and characteristic blue colour emitted under UV-light from azaindoles.



1.1 - acetophenone
1.2 - butyrophenone
1.3 - deoxybenzoin
1.4 - 4'-Dimethylaminoacetophenone
1.5 - 4'-methoxypropiophenone
1.6 - propiophenone

I.1 (R^1 = H, R^2 = H)
I.1.2 (R^1 = H, R^2 = CH_2CH_3)
I.1.3 (R^1 = H, R^2 = Ph)
I.1.4 (R^1 = $N(CH_3)_2$, R^2 = H)
I.1.5. (R^1 = OCH_3, R^2 = CH_3)
I.1.6 (R^1= H, R^2 = CH_3)

Scheme 56 – Conditions applied for the synthesis of azaindoles through one-pot ketone condensation/C–H activation reaction.

4.4. Preliminary computational studies: imine/enamine equilibrium of aminopyridines I and II.

Computational studies were performed by Prof Pedro Góis Lab (iMed, Faculty of Pharmacy, University of Lisbon). The procedure started with a preliminary conformation search with molecular mechanics (MM) using Schrödinger Maestro 11.1. Parameters used: force field OPLS3, solvent octanol, mixed torsional/low-mode sampling method built in the program. The low-energy conformers within 5 kcal mol^{-1} of the global minimum were saved and then optimized with DFT in Gaussian 09 Revision D.01. The geometries optimizations were carried out at the B3LYP-6-31G(d) level of theory. The vibrational frequencies were computed at the same level to check whether each optimized structure is an energy minimum or not and to evaluate its thermal corrections at 298K.

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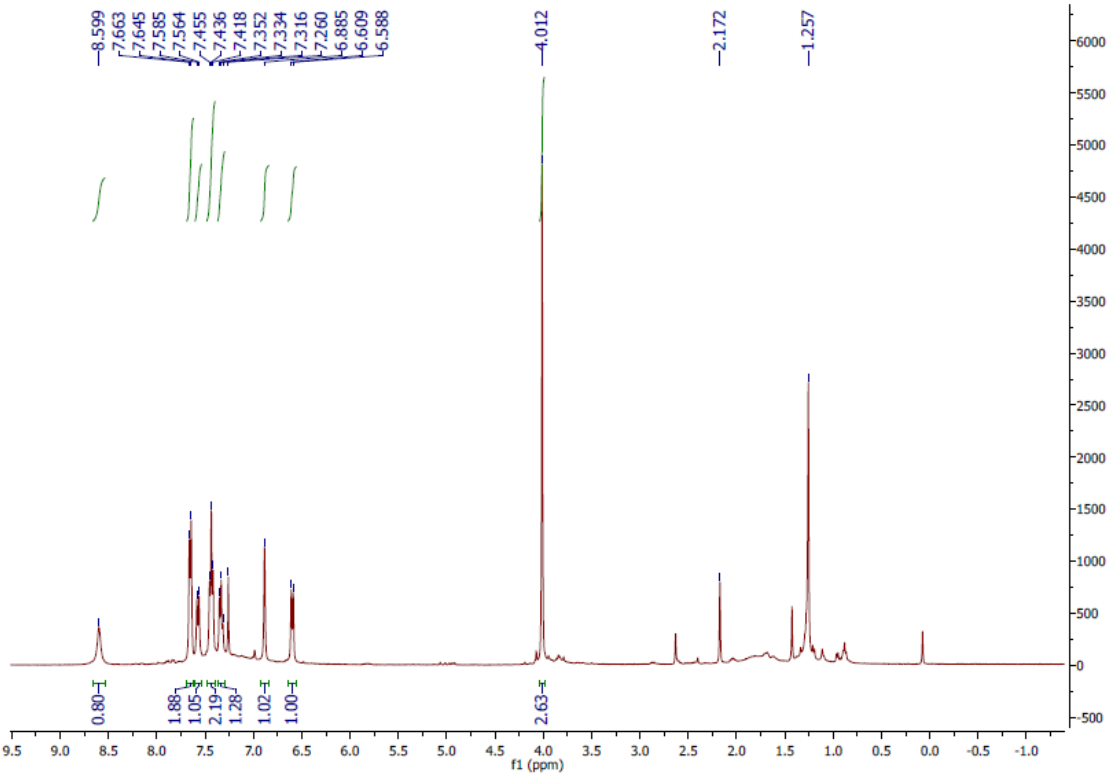
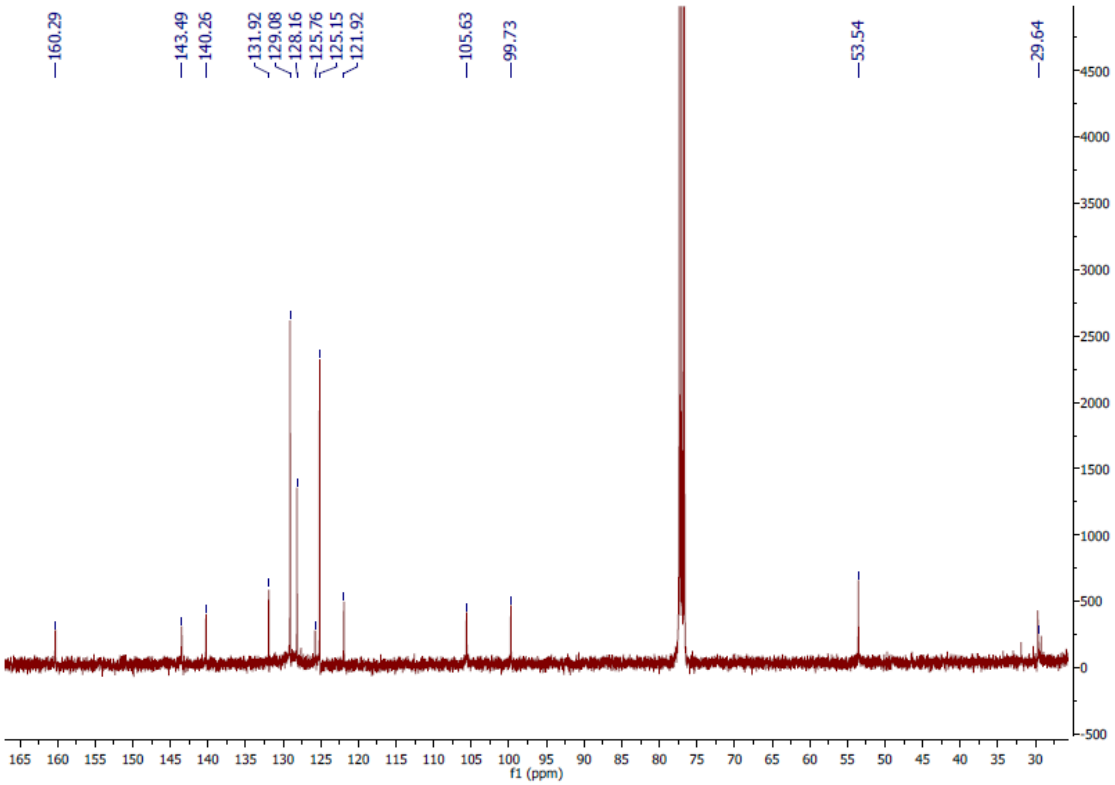
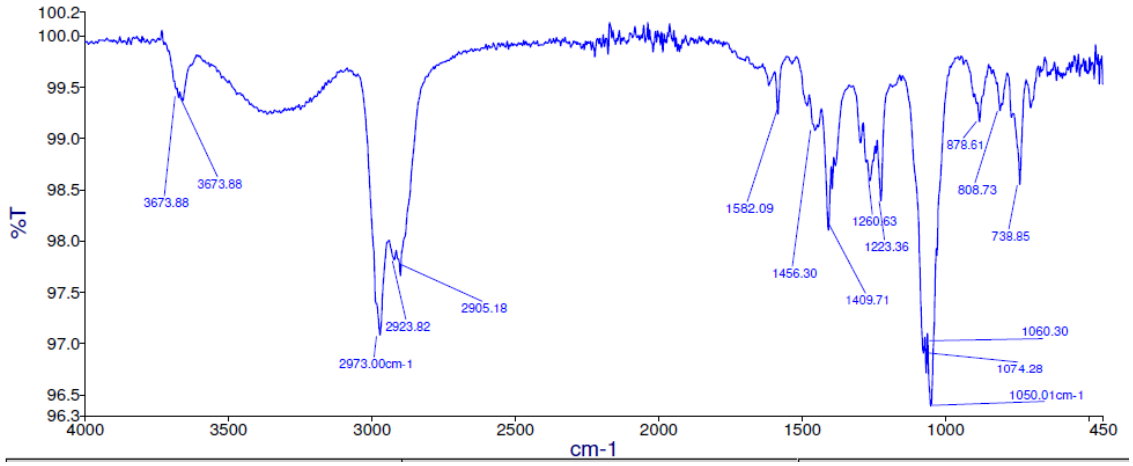
Appendix



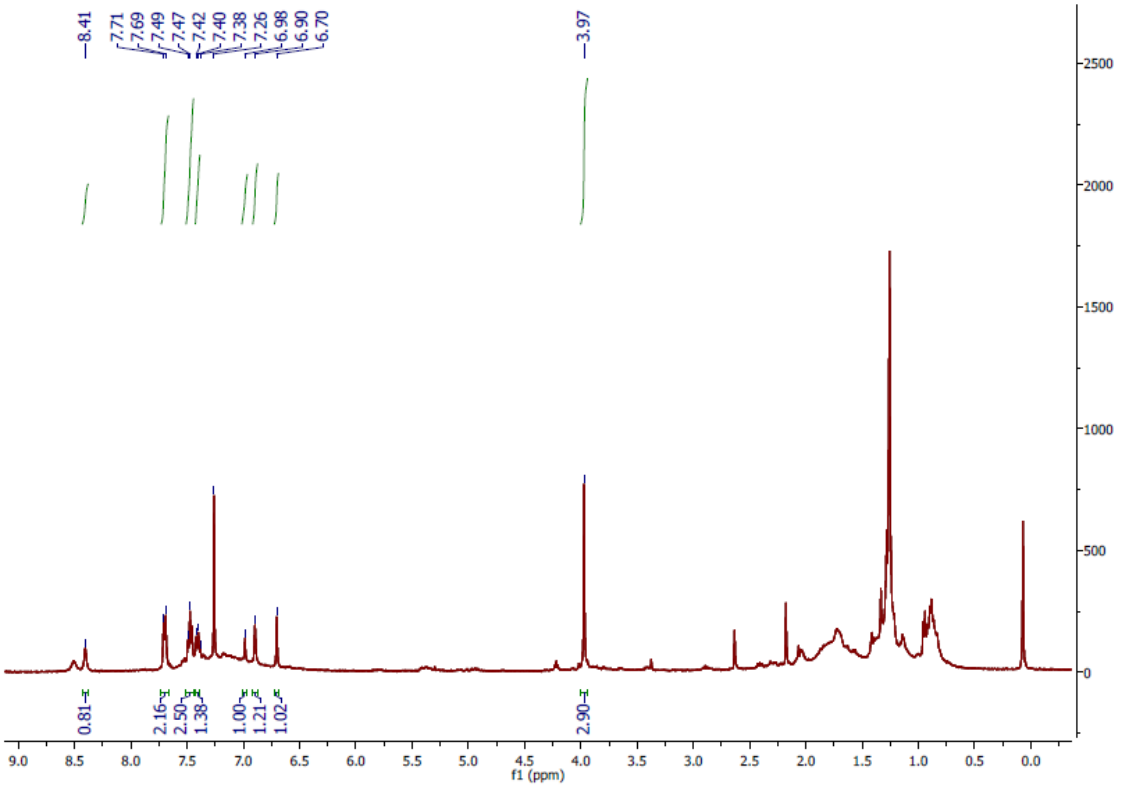
Spectrum 1 – ^{1}H NMR spectrum of 5-methoxy-2-phenyl-1*H*-pyrrolo[3,2-*b*]pyridine (**I.1**) in $CDCl_3$.



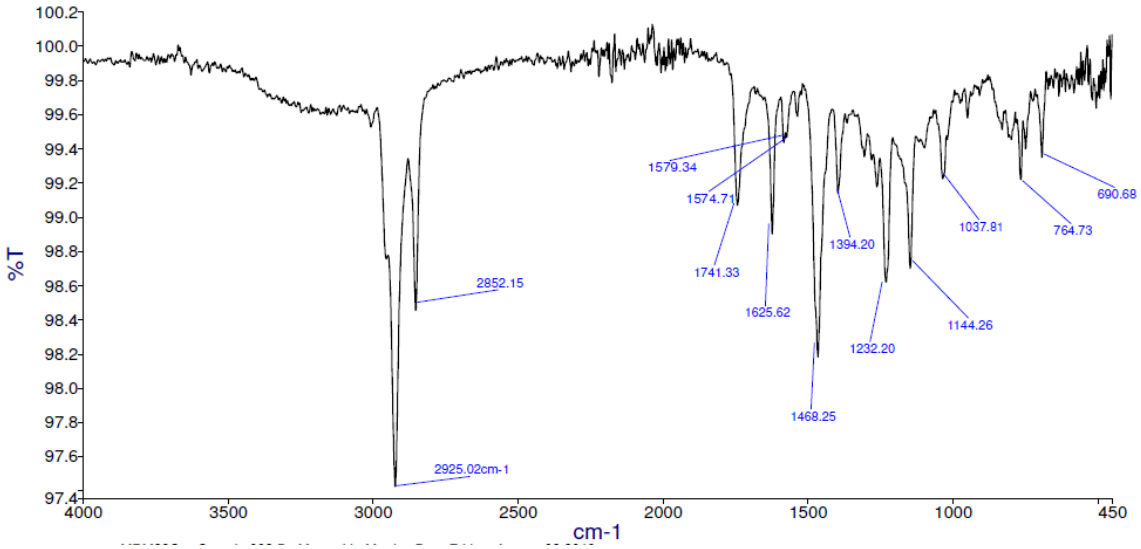
Spectrum 2 – ^{13}C NMR spectrum of 5-methoxy-2-phenyl-1*H*-pyrrolo[3,2-*b*]pyridine (**I.1**) in $CDCl_3$.



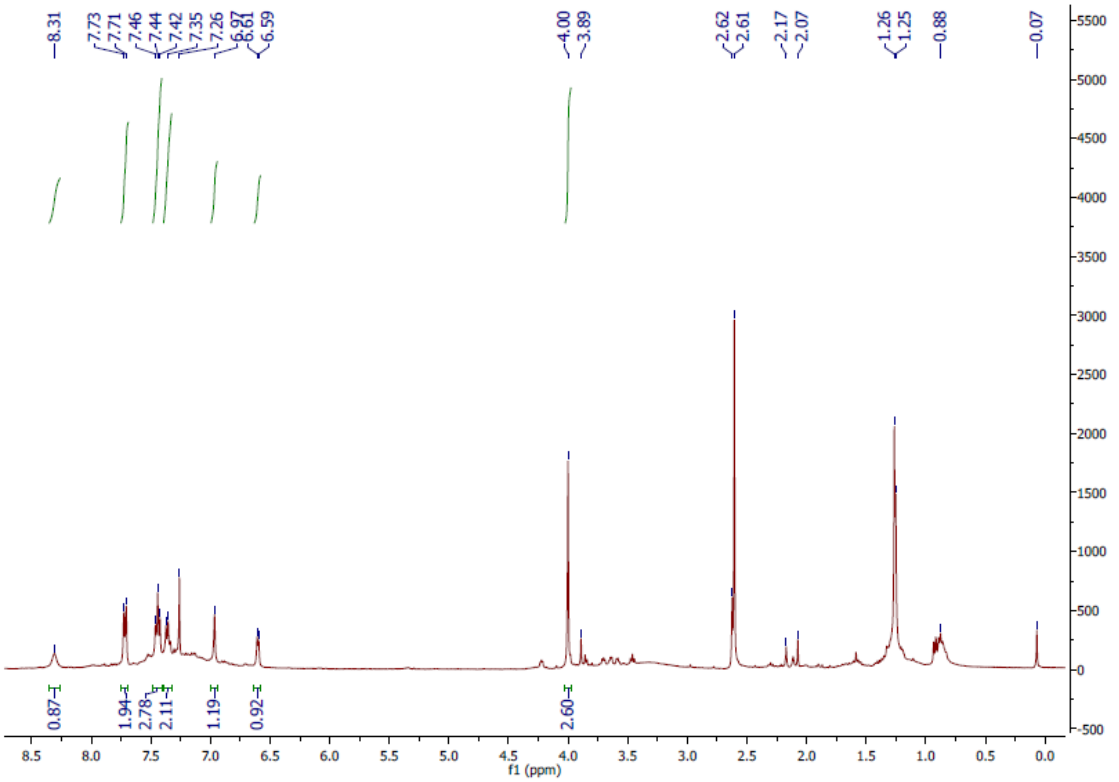
Spectrum 3 – ATR-FTIR spectrum of 5-methoxy-2-phenyl-1*H*-pyrrolo[3,2-*b*]pyridine (**I.1**).



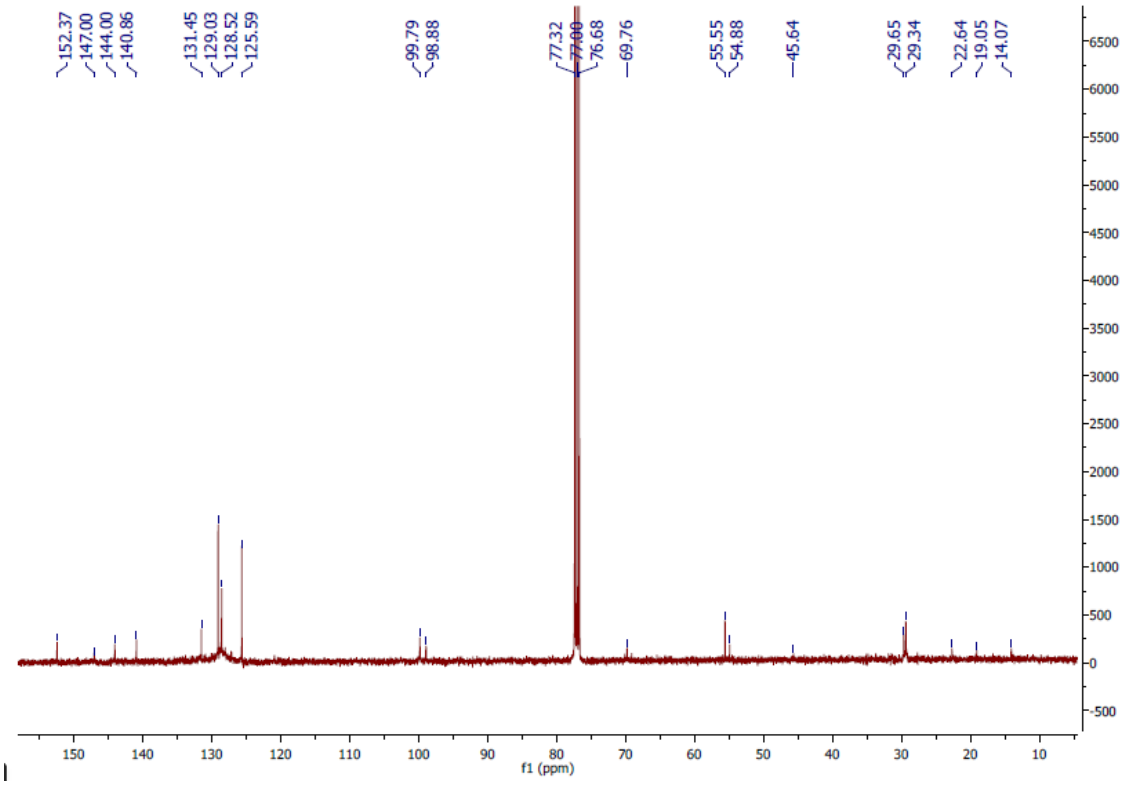
Spectrum 4 – ^{1}H NMR spectrum of 5-methoxy-2-phenyl-1*H*-pyrrolo[2,3-*c*]pyridine (**I.2**) in $CDCl_3$.



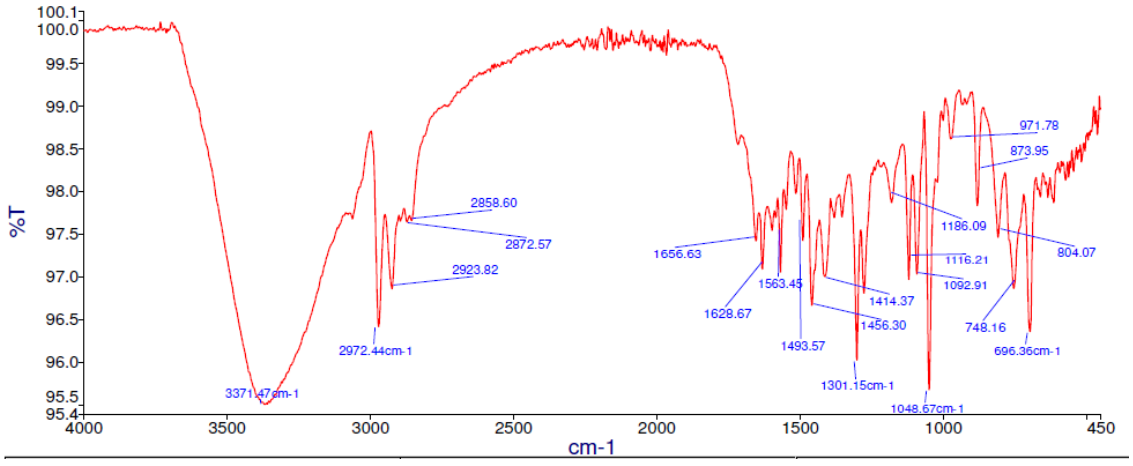
Spectrum 5 – ATR-FTIR spectrum of 5-methoxy-2-phenyl-1*H*-pyrrolo[2,3-*c*]pyridine (**I.2**).



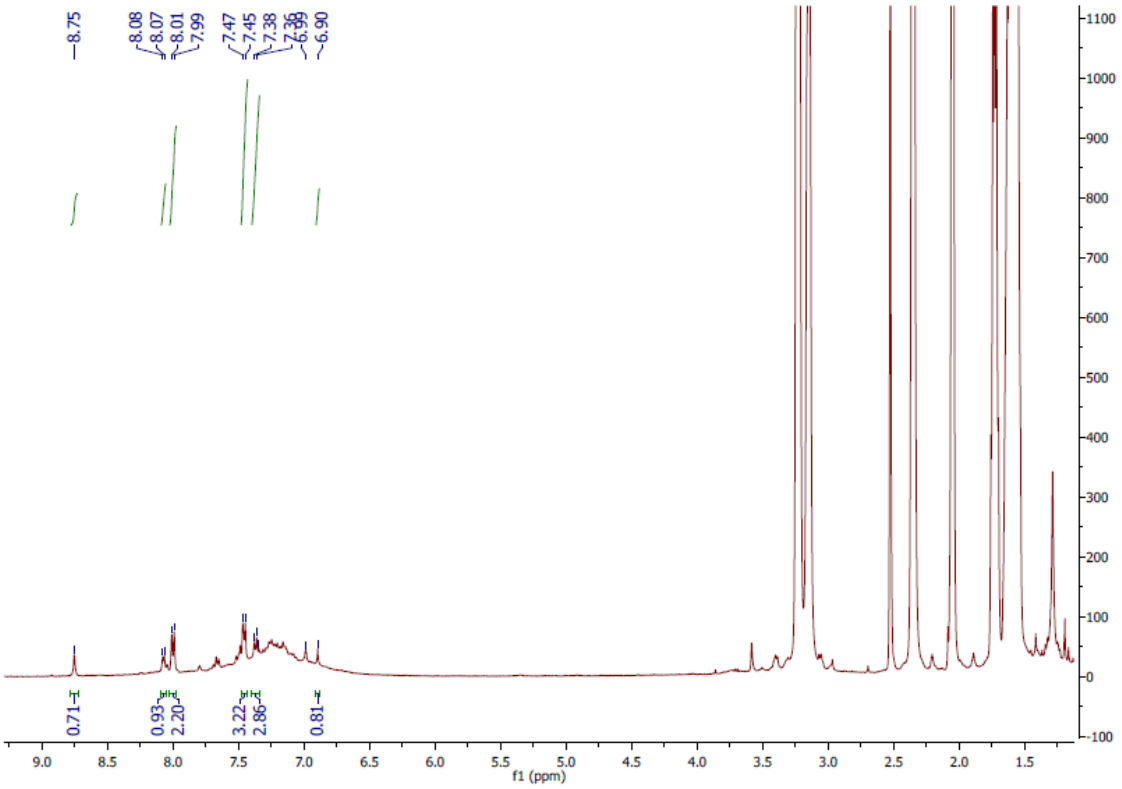
Spectrum 6 – ^{1}H NMR spectrum of 7-methoxy-2-phenyl-1*H*-pyrrolo[3,2-*b*]pyridine (**II.1**) in $CDCl_3$.



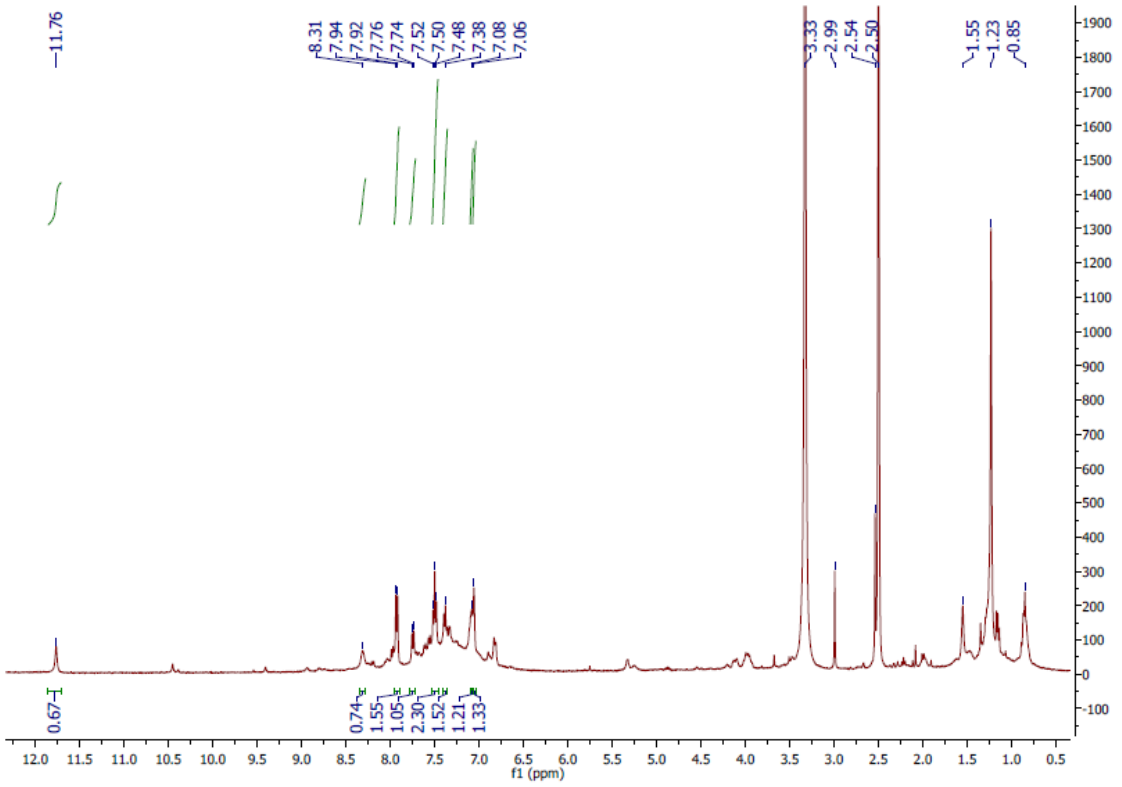
Spectrum 7 – ^{13}C NMR spectrum of 7-methoxy-2-phenyl-1*H*-pyrrolo[3,2-*b*]pyridine (**II.1**) in $CDCl_3$.



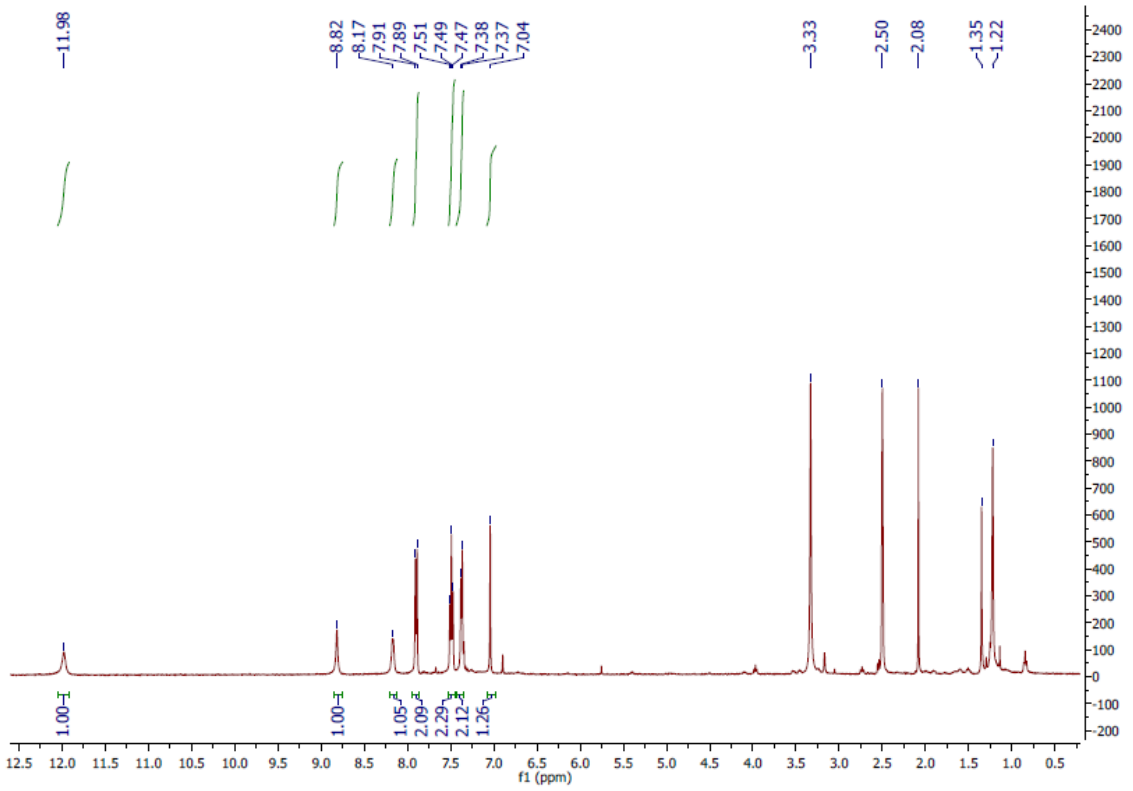
Spectrum 8 – ATR-FTIR spectrum of 7-methoxy-2-phenyl-1*H*-pyrrolo[3,2-*b*]pyridine **(II.1)**.



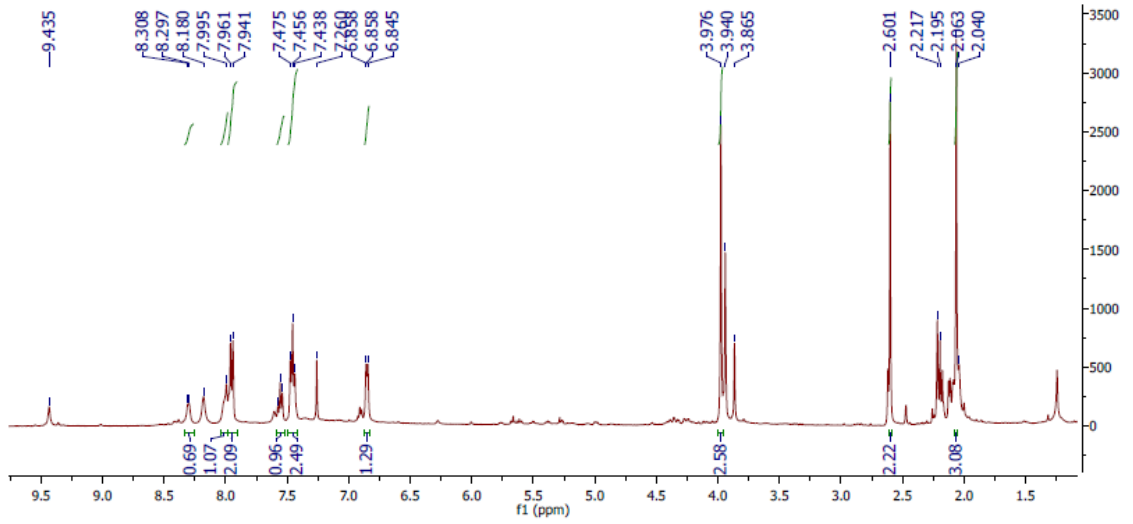
Spectrum 9 – ^{1}H NMR spectrum of 2-phenyl-1*H*-pyrrolo[2,3-*c*]pyridine (**III.1**) in acetone-d6 with a drop of DBU.



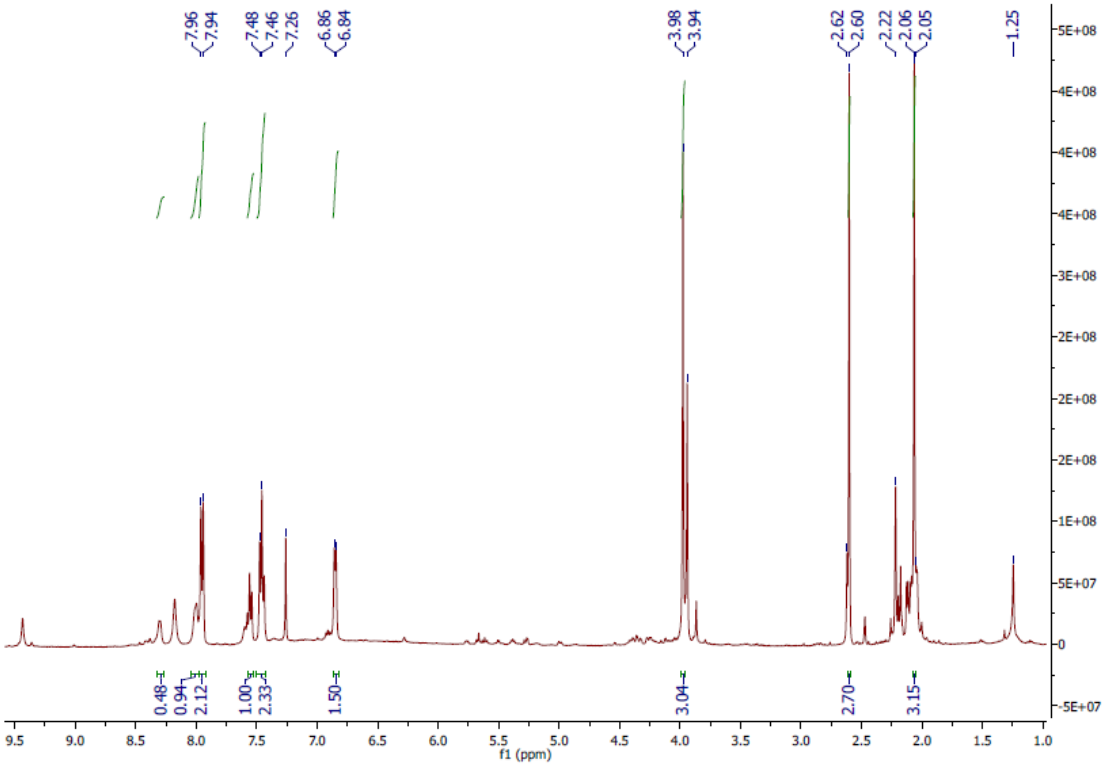
Spectrum 10 – ^{1}H NMR spectrum of 2-phenyl-1*H*-pyrrolo[3,2-*b*]pyridine (**III.2**) in DMSO-d6.



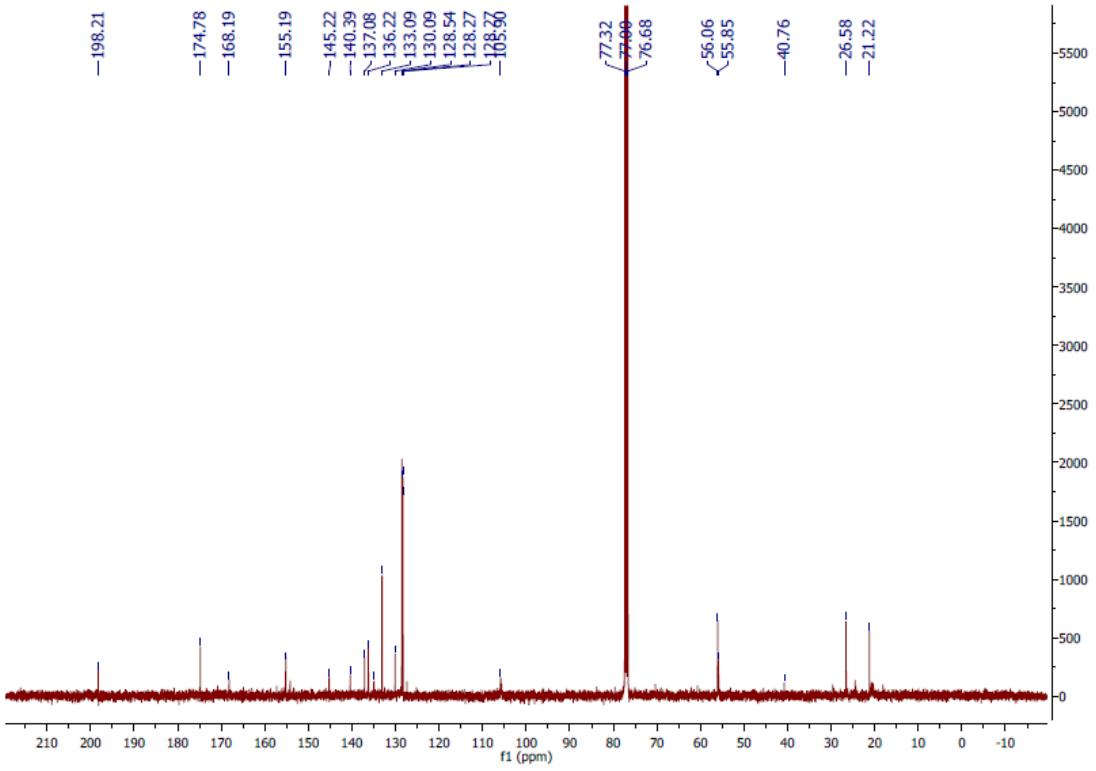
Spectrum 11 – ^{1}H NMR spectrum of 2-phenyl-1*H*-pyrrolo[3,2-*c*]pyridine (**IV.1**) in DMSO-d6.



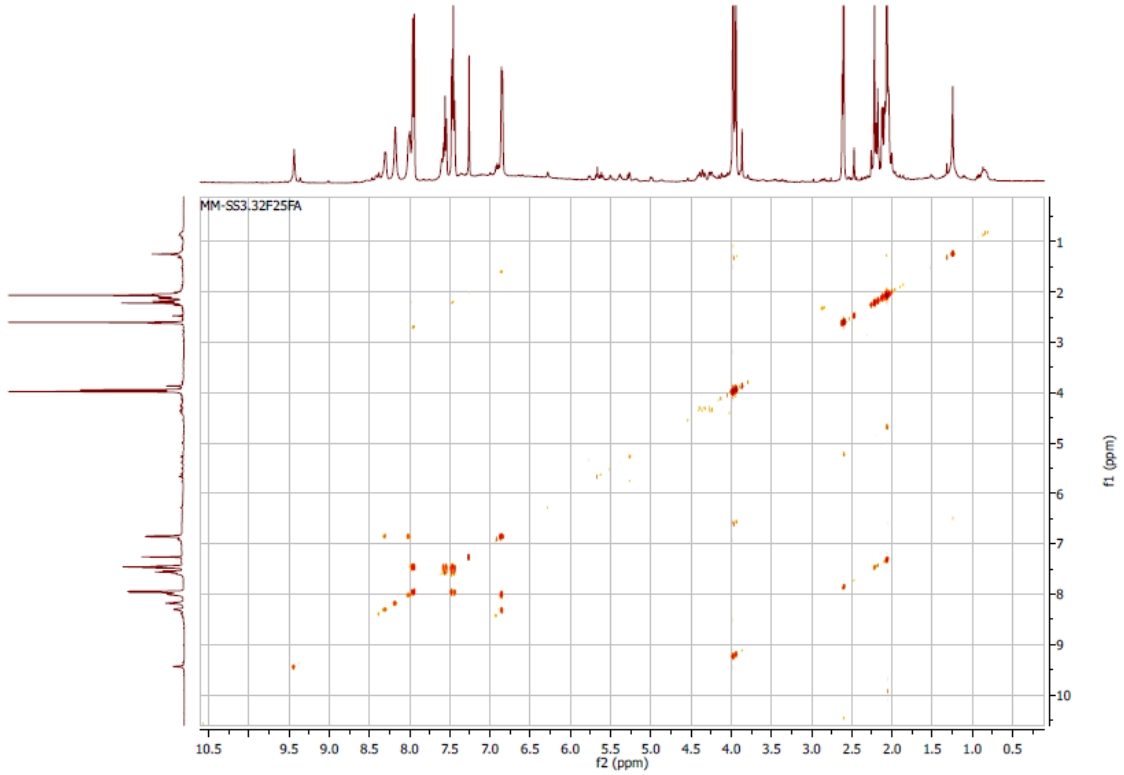
Spectrum 12 – ^{1}H NMR spectrum of (*E*)-4-methoxy-*N*-(1-phenylethylidene)pyridin-3-amine and palladium acetate chloride salt (**II.2**) in $CDCl_3$ performed after NMR sample preparation.



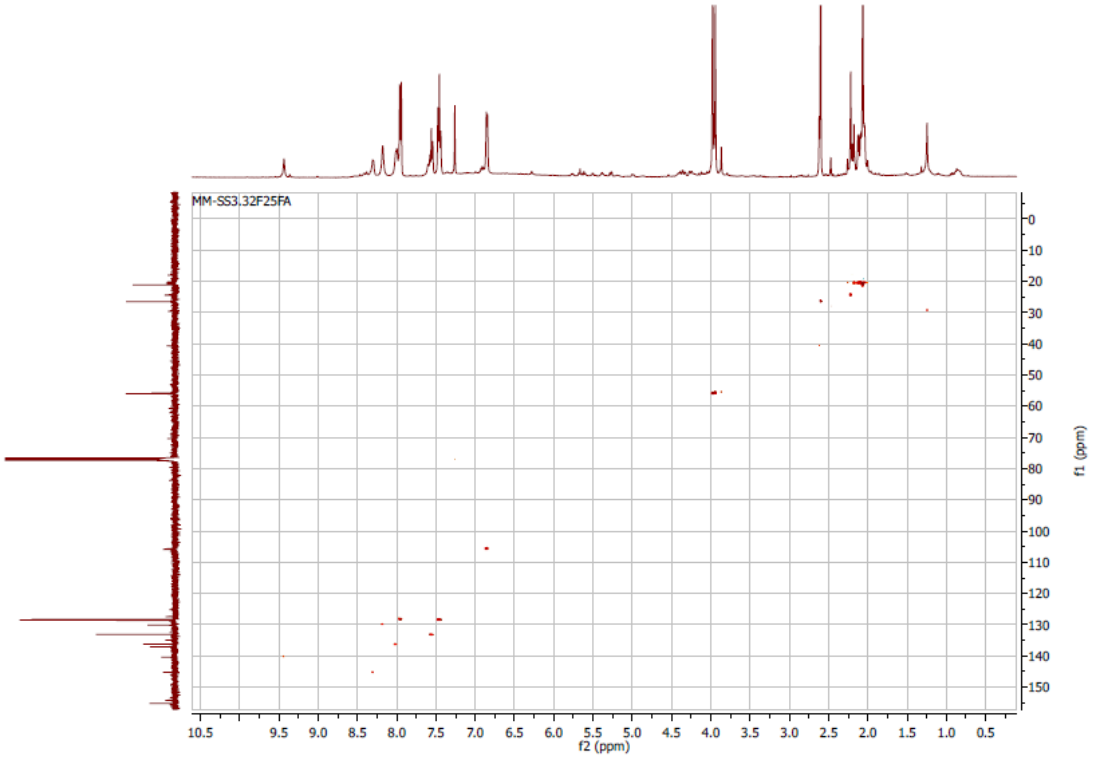
Spectrum 13 – ^{1}H NMR spectrum of (*E*)-4-methoxy-*N*-(1-phenylethylidene)pyridin-3-amine and palladium acetate chloride salt (**II.2**) in $CDCl_3$ after more than 24h in the NMR tube.



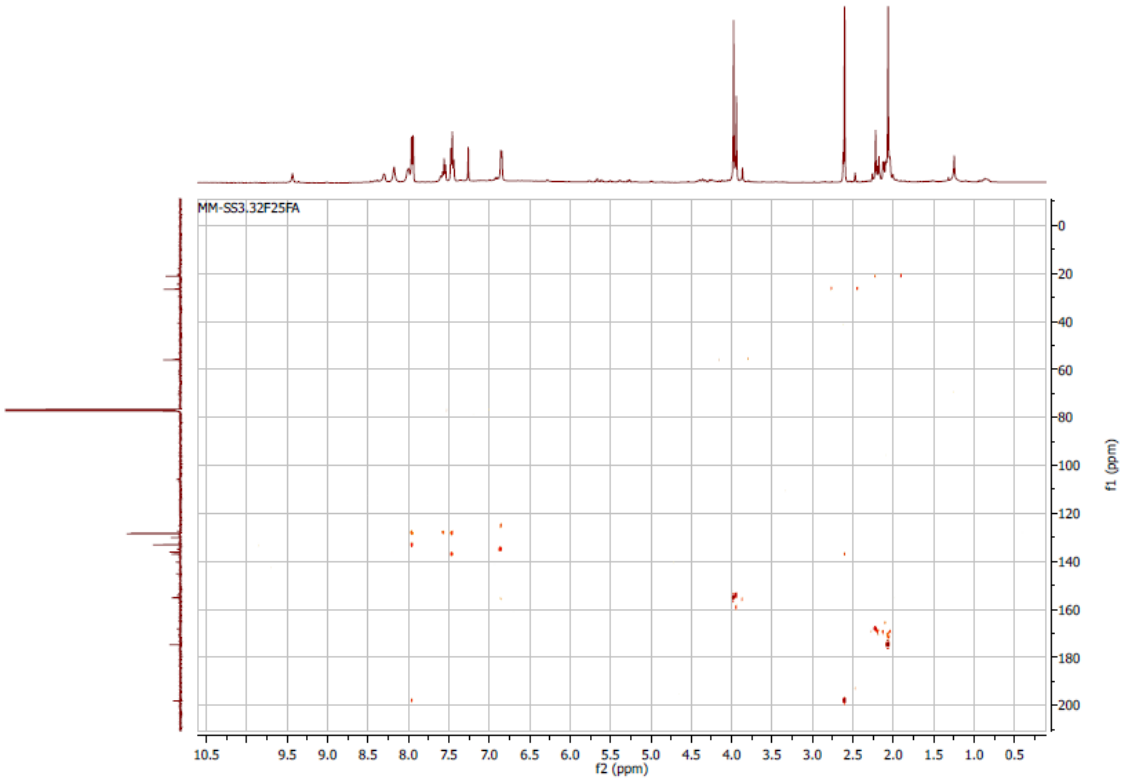
Spectrum 14 – ^{13}C NMR spectrum of (*E*)-4-methoxy-*N*-(1-phenylethylidene)pyridin-3-amine and palladium acetate chloride salt (**II.2**) in $CDCl_3$ after more than 24h in the NMR tube.



Spectrum 15 – COSY spectrum of (*E*)-4-methoxy-*N*-(1-phenylethylidene)pyridin-3-amine and palladium acetate chloride salt (**II.2**) in $CDCl_3$ after more than 24h in the NMR tube.



Spectrum 16 – HSQC spectrum of (*E*)-4-methoxy-*N*-(1-phenylethylidene)pyridin-3-amine and palladium acetate chloride salt (**II.2**) in $CDCl_3$ after more than 24h in the NMR tube.



Spectrum 17 – HMBC spectrum of (*E*)-4-methoxy-*N*-(1-phenylethylidene)pyridin-3-amine and palladium acetate chloride salt (**II.2**) in $CDCl_3$ after more than 24h in the NMR tube.