Synthesis of heterocycles *via* isocyanide-based multi-component reactions.

By

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A thesis submitted to the Department of Pure and Applied Chemistry, University of Strathclyde, in part fulfillment of the regulations for the degree of Master of Philosophy in Chemistry.

I certify that the thesis has been written by me. Any help I have received in my research work and the preparation of the thesis itself has been acknowledged. In addition, I certify that all information sources and literature used are indicated in the thesis.

September 2011

Acknowledgements

First of all, I would like to thank Prof. John Murphy for welcoming me into his group and for his advice during my entire stay, and Dr. Stuart Lang for the supervision of my project, and all his precious suggestions and support.

I would like to acknowledge all the members of the JAM group for their warm welcome, and the continuously enjoyable atmosphere in the laboratory, and more especially Ryan and Harry for their help on some technical points. I would also like to thank Zoe Hamilton for her contribution to the project. Also special thank to Steven, who has kindly accepted to run some of the calculations for me.

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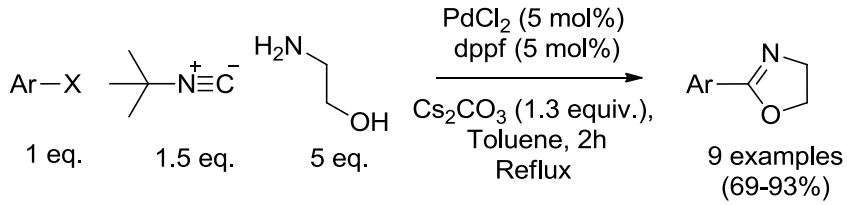
Abbreviations

Ac-	Acetyl
Bu -	Butyl
cm -	Centimetre
d -	Doublet
DCM -	Dichloromethane
DIC-	2,6-Dimethylphenyl-isocyanide
DMAc -	Dimethylacetamide
DMF -	Dimethylformamide
DMSO -	Dimethylsufoxide
dppf -	1,1'-Bis(diphenylphosphino)ferrocene
dppe -	1,2-Bis(diphenylphosphino)ethane
e.g. -	*Exempli gratia*
eq. -	Equivalent
Et -	Ethyl
et al. -	*Et alii*
ESI -	Electrospray ionisation
FT-IR -	Fourier transform – infrared
h -	Hour
HOMO -	Highest occupied molecular orbital
Hz -	Hertz
i.e. -	*id est*
J -	Coupling constant
IMCR -	Isocyanide based multi-component reaction
IR -	Infrared
MS -	Mass spectrometry
MCR -	Multi-component reaction
Me -	Methyl
min -	Minute
mol -	Mole
m.p. -	Melting point
Ms -	Mesyl (methanesulfonyl)

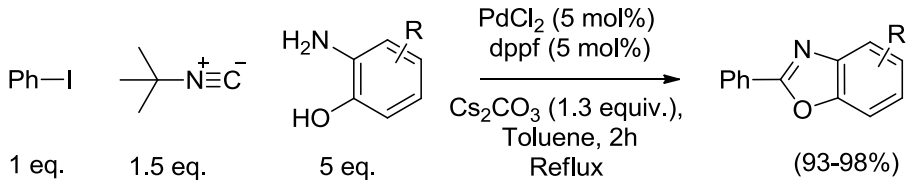
NMR -	Nuclear Magnetic Resonance
Ph -	Phenyl
ppm -	Parts per million
psig -	Pounds per square inch gauge(pressure)
r.t. -	Room temperature
s -	Singlet
t -	Triplet
tert -	Tertiary
Tf -	Triflyl (trifluoromethanesulfonyl)
THF -	Tetrahydrofuran
TIC -	*tert*-butylisocyanide
TLC -	Thin layer chromatography
Tol -	Tolyl
Ts -	Tosyl (toluenesulfonyl)
Xantphos -	4,5-Bis(diphenylphosphino)-9,9-dimethylxanthene
z -	Charge
°C -	Degrees Celsius
δ -	Chemical shift

Abstract.

This thesis deals with the development of a new multi-component reaction for the synthesis of heterocycles involving the process of insertion of isocyanides into a carbon-palladium bond. The application to the synthesis of oxazolines was explored and was shown to give good yields of 2-aryloxazolines. The reaction conditions developed use a $PdCl_2$/dppf catalytic system which enables the formation of an amidine intermediate. This intermediate then cyclises into the oxazoline. This reaction was performed on several aromatic systems, electron-rich or electron-poor, and appeared to be very tolerant of substitution pattern.

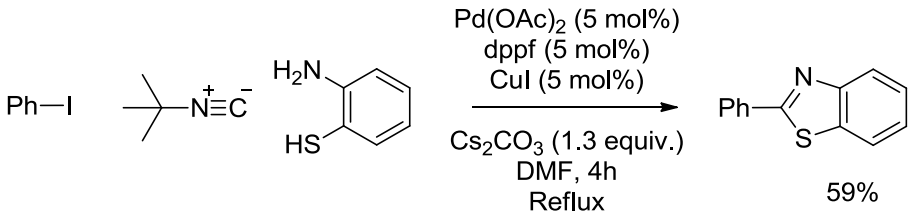


The extension of these conditions to the synthesis of 2-arylbenzoxazoles has been studied. Excellent yields have been obtained for this transformation which suggests that these conditions could be applied to the synthesis of different types of heterocycles.[1]



The application to the synthesis of 2-arylbenzothiazoles appeared to be more challenging as a different reactivity was observed. Indeed, the same reaction conditions afforded the unsubstituted benzothiazole. However, a slight modification

of the reaction conditions and the use of a copper species as co-catalyst enabled the 2-phenylbenzothiazole to be obtained. This required optimization in order to obtain a good yield for this transformation, and especially to prevent the Ullmann-coupling side-reaction from occuring. A yield of 59% which is noteworthy for a multi-component reaction, was finally obtained for the formation of 2-phenylbenzothiazole.

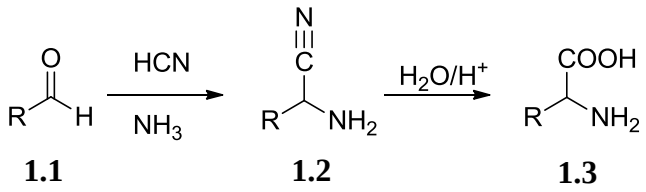


1 General introduction

1.1 Isocyanide multi-component reactions

Multi-component Reactions (MCRs) are convergent reactions, in which three or more starting materials react to form a product, which contains elements from all the starting materials. Although they are based on the same properties and principles, MCRs are fundamentally different than usual two-component organic reactions. The MCRs have the crucial advantage of avoiding some of the negative aspects of multistep synthesis, such as preparative complexity or multiple isolation/purification steps. This makes them one of the most useful tools for the synthesis of libraries of a large number of compounds.

Historically, the Strecker synthesis of amino acids, first published in 1850,[2] is generally considered as the first MCR reaction. This reaction consists in the reaction of ammonia and hydrogen cyanide with an aldehyde **1.1** to give the α-aminonitrile **1.2**, which was hydrolyzed to the α-aminoacid **1.3** (Scheme 1).



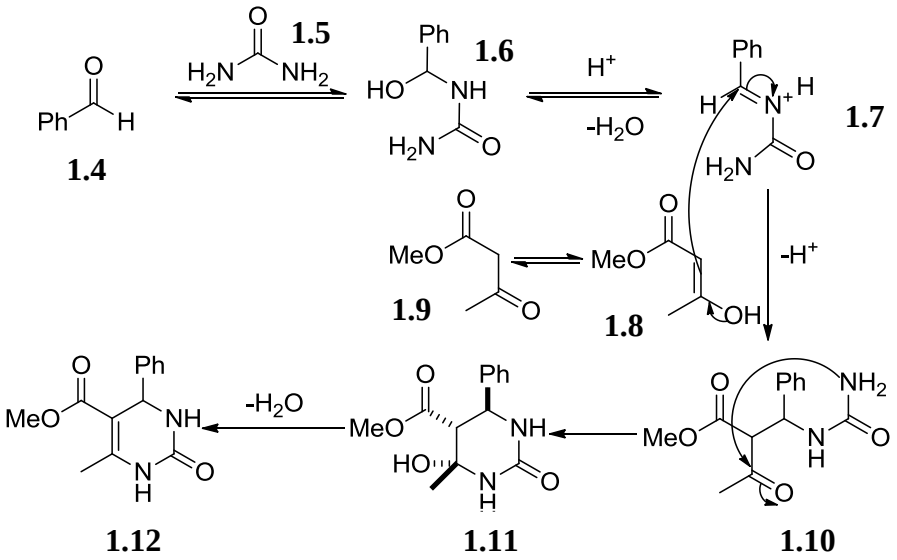
1.1 **1.2** **1.3**

Scheme 1 : Strecker synthesis of α-aminoacids.

This reaction generates a new stereogenic centre. A large number of asymmetric Strecker reactions have been developed, which Yet highlighted in a review.[3]

The first synthesis of an heterocycle *via* a MCR is the synthesis of dihydropyrimidines described by Biginelli[4] in 1893 (Scheme 2). It consists of an acid-catalyzed cyclocondensation reaction of methyl acetoacetate **1.9**, benzaldehyde

1.4 and urea **1.5**. The mechanism of this transformation has been extensively investigated by Kappe who detailed a complete mechanism[5] in 1997 (Scheme 1.2). According to this mechanism, the reaction starts with the acid-catalyzed condensation of the urea **1.5** on the aldehyde **1.4**. The enol form **1.8** of the keto-ester **1.9** reacts with the *N*-acylium ion **1.7**, to give the intermediate **1.10** which cyclises into **1.11**. The elimination of a molecule of water afford the dihydropyrimidone product **1.12**.



Scheme 2 : Mechanism of the Biginelli reaction.

The elucidation of this mechanism has triggered the development and optimization of hundreds of new reaction conditions for this transformation using a Lewis acid as a catalyst.[6] Moreover, the pharmacological interest of the dihydropyrimidine scaffold[7] makes this reaction extremely useful in the field of drug discovery.

One important subsection of MCR is the isocyanide-based MCR (IMCR). This type of reaction uses the uncommon but rich chemistry of the isocyanide functional group.[8] Isocyanides are one of the rare stable organic species to possess a formally divalent carbon. Only carbon monoxide, which is isoelectronic to isocyanide, and carbenes share this characteristic, however carbenes are known to be a really short-

lived species. Many natural products containing an isocyanide group have been identified, most of them extracted from marine species.[9] Their chemistry is characterized by three major properties: α-acidity, easy formation of radicals, and the reactivity of electrophiles and nucleophiles with the terminal carbon. This last property is the most important regarding the use of isocyanides in MCR. Most organic small molecules react with electrophiles and nucleophiles at different sites in the molecule.

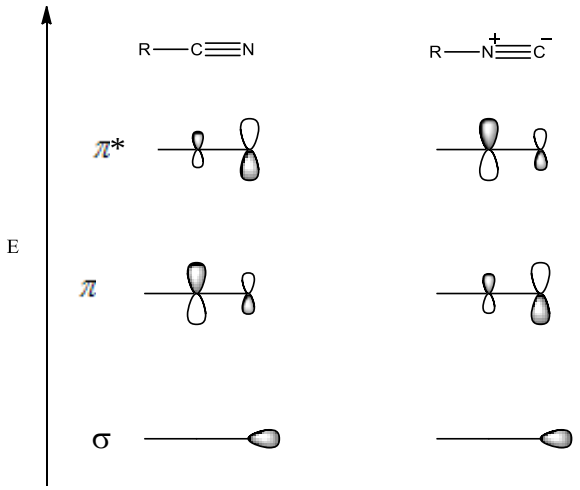
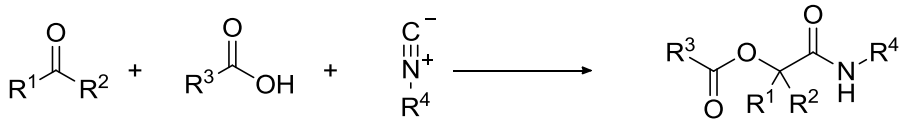


Figure 1 : Qualitative comparison of frontier orbitals between Isocyanides and Nitriles

While reacting with nucleophiles, isocyanides react with their π* orbitals, at the carbon which has the lower orbital coefficient for this. When the isocyanide reacts with an electrophile, it reacts using its σ orbital, so here again it reacts at the carbon, contrary to the nitrile which reacts with the nitrogen. Only carbenes and carbon monoxide share this property. Therefore this has been widely used in the development of multicomponent synthesis.[8]

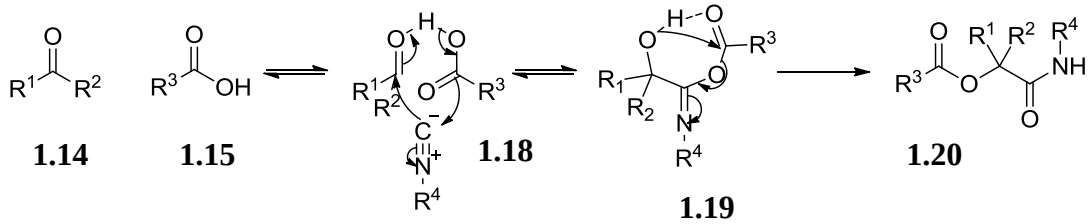
Passerini[10] was the first to develop and publish an isocyanide-based MCR (IMCR) in 1921 (Scheme 3). He detailed the synthesis of α-hydroxy carboxamides through the reaction of a carboxylic acid **1.15**, a carbonyl group **1.14** (either aldehyde or ketone) and an isocyanide **1.16**.



1.14 **1.15** **1.16** **1.17**

Scheme 1.3: The Passerini reaction.

The mechanism of this 3-component reaction has been discussed by Ugi[11] who discovered that the reaction was accelerated in aprotic solvent, which indicates a non-ionic mechanism (Scheme 4). He then postulated a concerted mechanism for this reaction where hydrogen bonding between the aldehyde **1.14** and the carboxylic acid **1.15** in the transition state **1.18** is believed to be important. This mechanism shows the importance of the divalent carbon atom of the isocyanide **1.16**. This acts as a nucleophile while attacking the carbonyl electrophile carbon and as an electrophile as it is attacked by the nucleophilic oxygen of the acid. The resulting intermediate **1.19** rearranges into the more stable α-acyloxycarboxamide **1.20**.



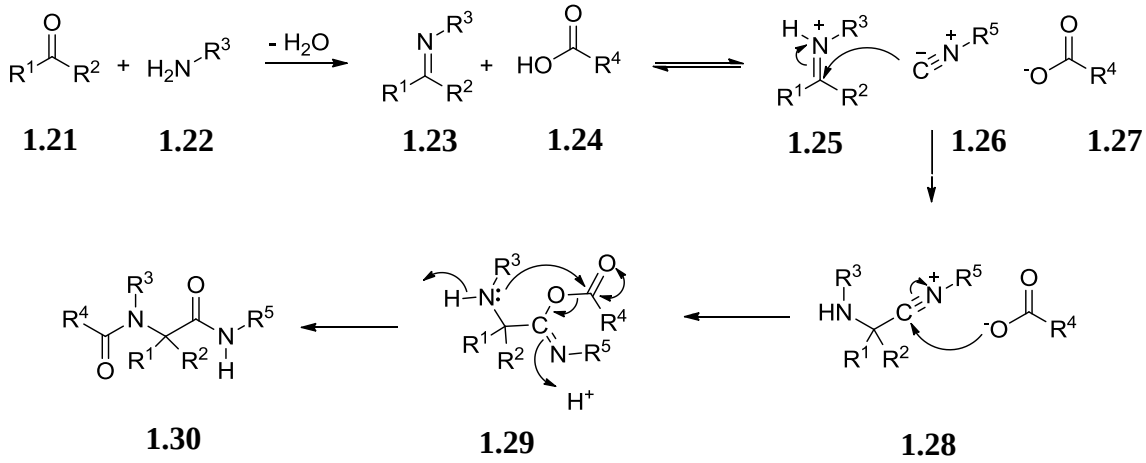
1.14 **1.15** **1.18** **1.19** **1.20**

Scheme 4: Mechanism of the Passerini reaction

Several modifications of these reaction conditions have been developed for the formation of heterocycles such as benzothiophenes[12] or oxazoles.[13] Frey published the first examples of a highly stereoselective Passerini reaction[14] whereas Denmark[15] developed the first catalytic asymmetric Passerini reactions.

Ugi[16] also designed a four-component IMCR, which involved the reaction of an amine **1.22** (secondary or primary), an aldehyde **1.21** (or ketone), a carboxylic acid and an isocyanide **1.26** to afford an α-aminoacyl amide derivative **1.30** (Scheme 5).

The mechanism involves the formation of the imine **1.23** by the condensation of the amine on the aldehyde, and then the reaction of this imine with the two other components is comparable to the reactivity observed in the Passerini reaction. Indeed, side-products obtained by the Passerini reaction between the substrates can be observed. The pre-formation of the imine intermediate can be a way to avoid the formation of these products. The reaction is exothermic and quite rapid at room temperature, which makes it ideal for parallel and automated synthesis.



Scheme 5 : Mechanism of the Ugi reaction.

The Ugi four-component reaction finds its principal application in the synthesis of peptides and α-aminoacids,[17] and its potential synthetic power for natural product synthesis has been proven, by Joullié for the synthesis of (+)-furanomycin **1.31** (Figure 2).[18] However, the original reaction has been modified several times for the synthesis of various heterocycles.[19]

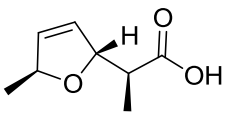
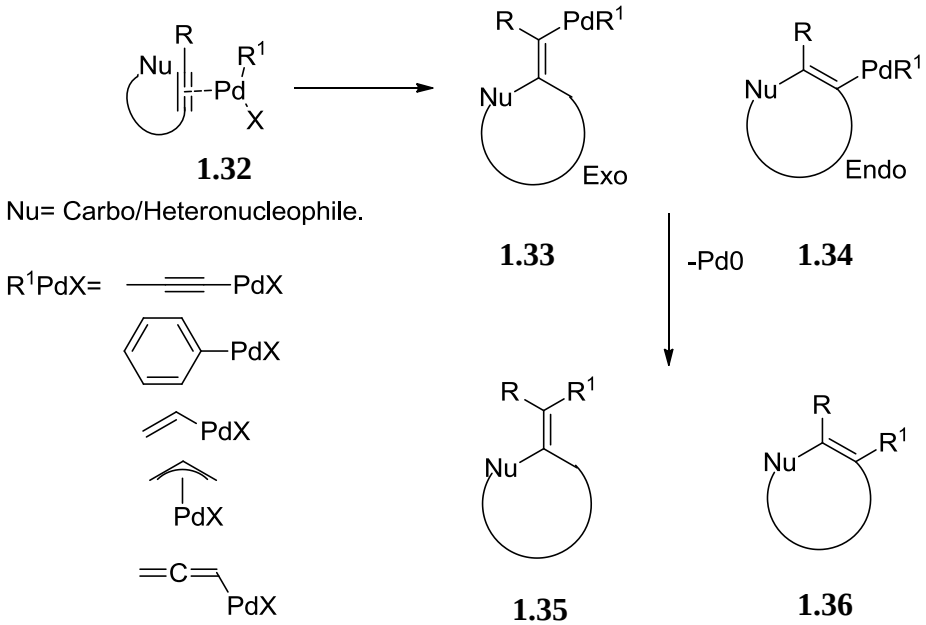


Figure 2: (+)-furanomycin

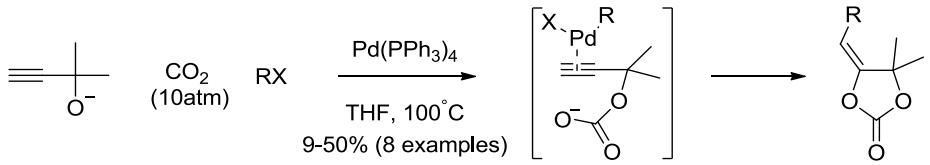
1.2 Palladium catalysis in multicomponent synthesis of heterocycles.

The 2010 Nobel prize award (for R. Heck, E-I. Negishi and A. Suzuki) has shown that palladium catalysis has become one of the major tools for synthetic organic chemistry. Therefore, with the growing interest in MCRs, several multi-component syntheses using palladium-catalyzed methods have been developed in the past 2 decades. Balme *et al.* have highlighted some of the most remarkable examples in 2003 for the Pd-assisted multi-component synthesis of carbocycles, and in 2006 for the synthesis of heterocycles.[20] In these reviews, they focused their discussion on new methods involving the reactivity of unsaturated compounds (alkenes, alkynes and allenes). The palladium-catalysed cyclisation reaction between an alkyne or alkene and a nucleophile in the same molecule is described. This consists of a Wacker-type[21] oxidative addition of the Pd species at the unsaturated bond **1.32** which activates this bond for the nucleophilic attack. The intramolecular pathway leads to the *exo* **1.35** or *endo* **1.36** cyclised compound after reductive elimination of the palladium (Scheme 6).



Scheme 6: Pd-catalyzed cyclisation of alkyne-containing substrates

Therefore many MCRs using this type of process have been published in the last two decades, starting with Inoue *et al.* in 1990 with their synthesis of cyclic vinylidene carbonates,[22] from the reaction of a propargylic alkoxide **1.37** with carbon dioxide (Scheme 7). The cyclisation of the monoalkylcarbonate through a palladium catalysed mechanism as described above leads to the dioxolane-2-one **1.39**.

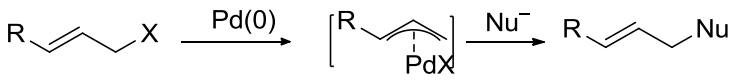


1.37 **1.38** **1.39**

Scheme 7: Inoue synthesis[22] of dioxolane-2-one **1.39**.

Since this piece of work, similar methods for the synthesis of heterocycles via a Pd-catalysed MCR have been described. Cyclisation leading to tetrahydrofurans,[23] cyclic ethers,[24] furans,[25] cyanoindoles[26] or benzofurans,[27] for instance, were developed. All of these used the same principle of the coordination of the palladium with the unsaturated bond to activate it for cyclisation. This makes it a powerful method for the multicomponent synthesis of heterocycles.

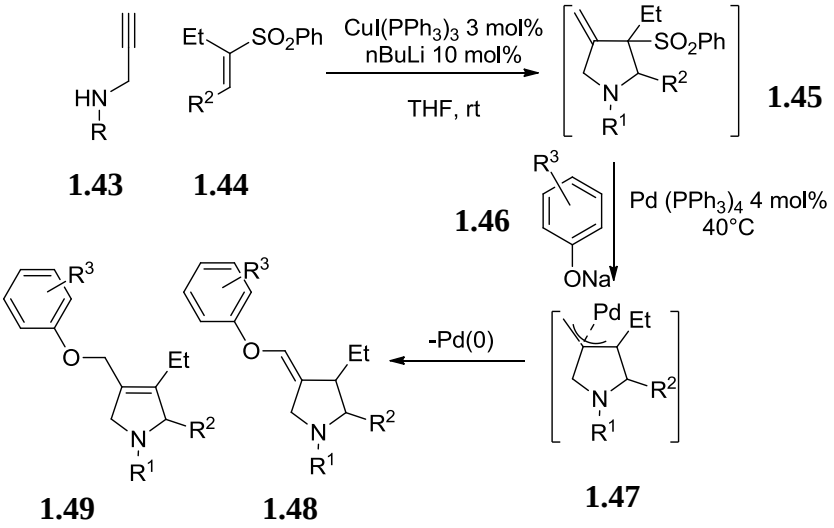
Another method using Pd-catalysis which has been used to develop new MCR leading to heterocycles is the displacement of allylic compounds *via* the formation of a π-allylpalladium complex (Scheme 8). This follows directly the work of Tsuji and Trost, who first described this process.[28] It involves firstly the coordination of the Pd(0) catalyst with the unsaturated compound **1.40**, followed by the oxidative addition where the leaving group X is expelled. The resulting π-allylpalladium species **1.41** undergoes the addition of a nucleophile, which usually occurs on the less hindered face of the complex to give the resulting product **1.42**.



1.40 **1.41** **1.42**

Scheme 8: Formation and reactivity of π-allylpalladium complex

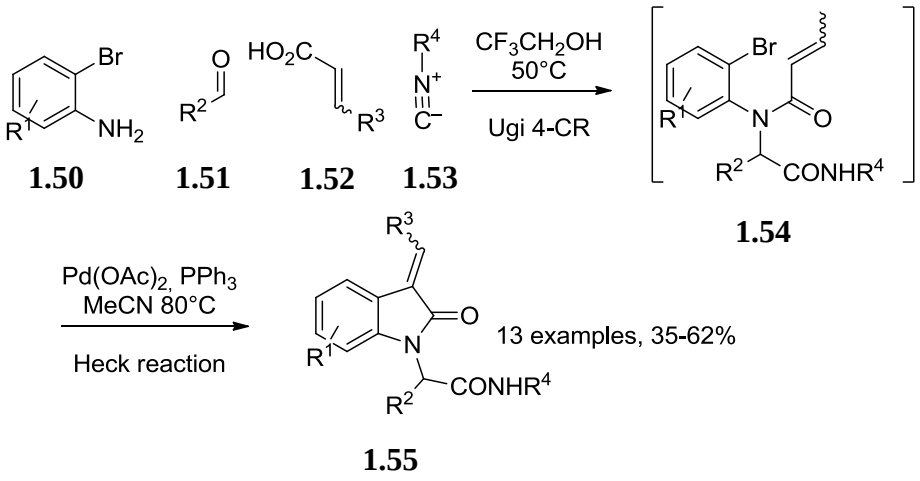
Balme *et al.* have employed this process for the multi-component synthesis of poly-substituted pyrroline **1.49** and their isomeric pyrrolidines **1.48** (Scheme 9).[29] This synthesis involves two metal-catalyzed reactions. The first consists of a cycloaddition between a propargylic nucleophile **1.43** and an electron-poor olefin catalyzed by copper. When the electron-deficient olefin is a vinylsulfone **1.44**, the displacement of this group and the formation by a π-allylpalladium complex **1.47** has been observed. This intermediate can then undergo the attack of a nucleophile, here a sodium phenolate derivative **1.46**, to give the pyrrolidine **1.48** and the pyrroline **1.49** in a one-pot process.



Scheme 9: Synthesis of pyrrolines and pyrrolidines.

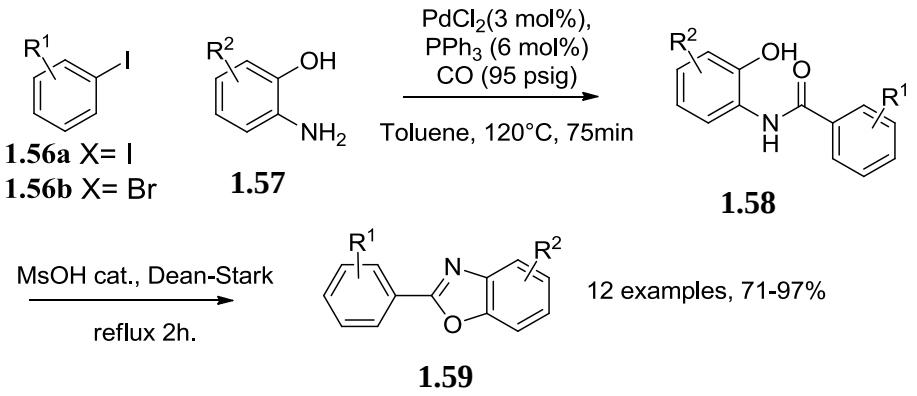
The Heck reaction has also been adapted to multicomponent heterocycle synthesis. One of the most remarkable examples was published in 2006 by Umkehrer *et al.*, who described a combination of the Ugi four-component reaction and the Heck reaction to allow the cyclisation of the product in a one-pot procedure (Scheme

10).[30] They started from a 2-bromoaniline **1.50** as one of the Ugi 4CR starting materials, which then afforded a *N*-bromophenylacrylamide **1.54**. This intermediate undergoes an intramolecular Heck reaction to cyclise into the alkylated indolone **1.55**. This work shows that coupling reactions such as the Heck reaction can be a powerful tool when linked with multi-component reactions.



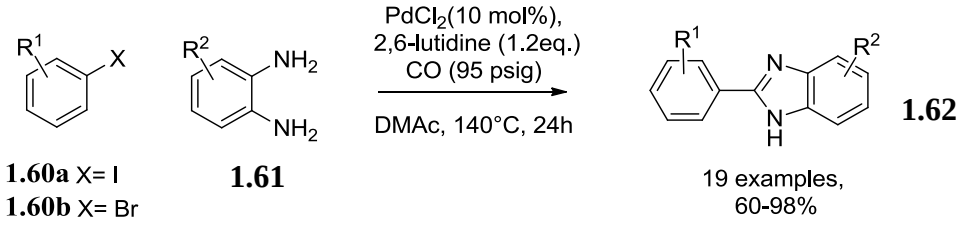
Scheme 10: Synthesis of *N*-alkylated indolones.

Most of the established palladium-catalysed reactions can be adapted to the multicomponent synthesis of heterocycles. However, one of the most prolific and suitable palladium-catalysed processes for MCR is carbonylation through carbon monoxide insertion. This process has been intensively studied[31] and is nowadays well known and widely employed in industry. Regarding the multi-component synthesis of heterocycles, the first to take advantage of this process were Perry and co-workers in 1991 (Scheme 11).[32] They developed the synthesis of 2-arylbenzoxazoles **1.59** from aryl halides, carbon monoxide and *ortho*-aminophenols **1.57**. The aryl halide **1.56** undergoes an oxidative addition of the palladium species, which is followed by the insertion of the carbon monoxide to the C-Pd bond. A nucleophilic addition by the aminophenol **1.57** on the newly formed acylpalladium complex affords the (2-hydroxyphenyl)amide **1.58**. The intramolecular condensation on the amide carbonyl group leads to the formation of the 2-arylbenzoxazole **1.59**. This condensation was catalysed by methanesulfonic acid.



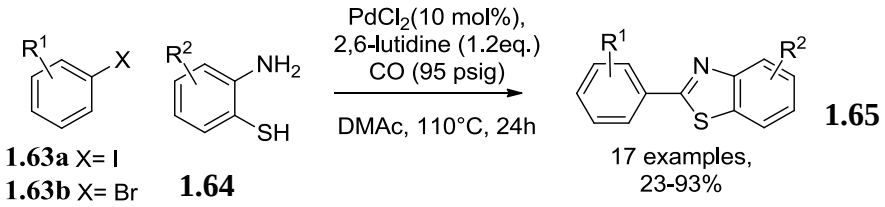
Scheme 11: Synthesis of 2arylbenzoxazoles

Two years later, they published the application of this method to the synthesis of 2-arylbenzimidazoles **1.62**, using aryl halides **1.60** and *o*-phenylenediamines **1.61**.[33] A similar procedure was employed, but the cyclisation step was this time performed under basic conditions (Scheme 12).



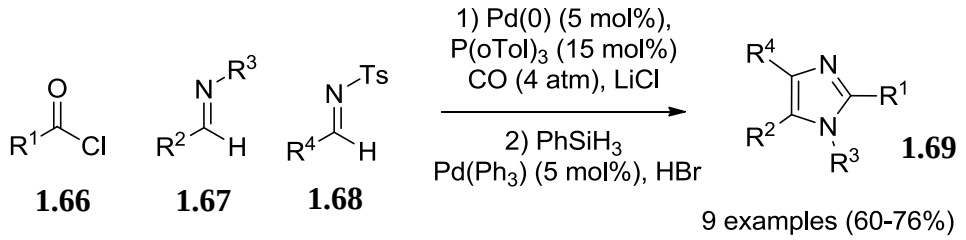
Scheme 12: Synthesis of 2-arylbenzimidazoles

One more year later, they published the application of the above method to the synthesis of 2-arylbenzothiazoles **1.65** from aryl halides **1.63** and *o*-aminothiophenols **1.64** (Scheme 13).[34]

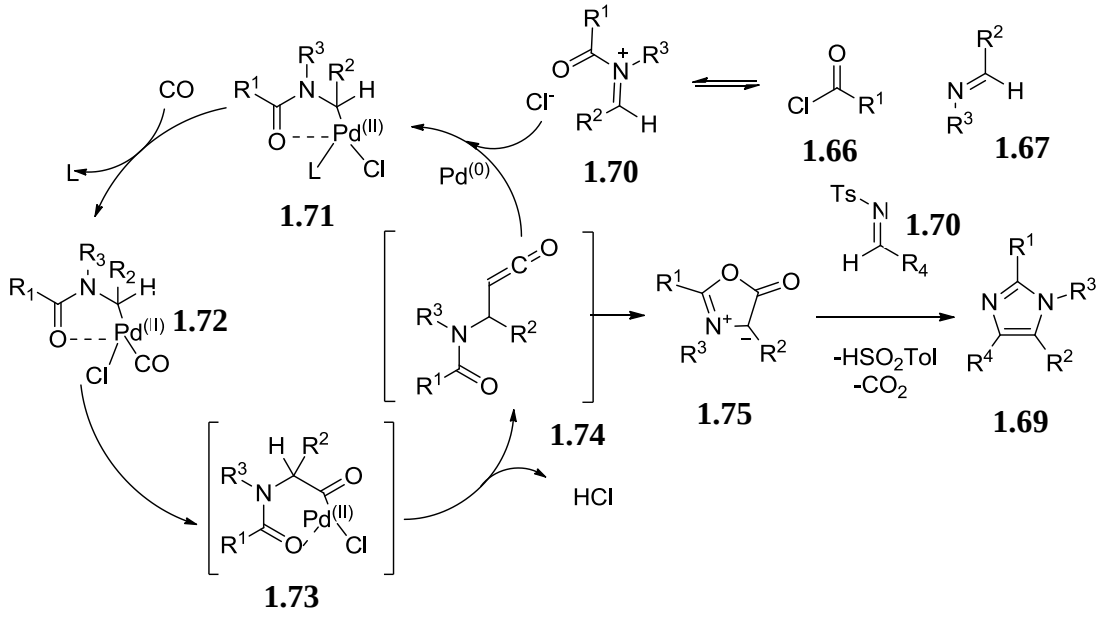


Scheme 13: Synthesis of 2-arylbenzothiazoles

Arndsten and Siamaki have been good contributors to this field in the last decade. For instance, in 2006, they described the one-step synthesis of tetrasubstituted imidazoles **1.69** from imines **1.67**/**1.68** and acid chlorides **1.66** (Scheme 14).[35] This reaction was based on their previous discovery of the synthesis of 1,3-oxazolium-5-olates (Munchnones) **1.75** from a palladium-catalyzed coupling between imine **1.67**, acyl chloride **1.66** and carbon monoxide. Therefore they applied the same method, adding a tosyl-imine **1.68** substrate considering that it should undergo a 1,3-dipolar cycloaddition with the Munchnones **1.75** synthesized *in situ*. They proposed a mechanism following this logic (Scheme 15).



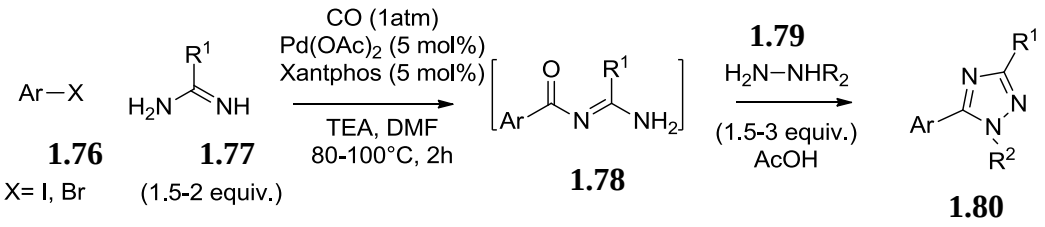
Scheme 14: Synthesis of tetrasubstituted imidazoles



Scheme 15: Mechanism proposed by Arndsten *et al.*[35]

On the same principle, the Arndtsen group also developed a palladium catalysed multi-component synthesis of β-lactams[36] and imidazolones[37] from the same starting materials.

Recently Staben and Blaquiere published an elegant synthesis of fully substituted triazoles **1.80** from aryl halides **1.76**, hydrazines **1.79** and amidine **1.77** *via* a multicomponent carbonylative heterocyclization process (Scheme 16).[38] This process involves easily accessible starting materials, palladium catalyst and ligand to afford a trisubstituted triazole ring, where all the substituents can be varied. This reaction goes through a key intermediate **1.78** which is the product of the carbonylative coupling between aryl halides **1.76** and amidine **1.77**. The interest of this synthesis is that it is highly tolerant towards the nature of the amidine, the aryl group and the hydrazine **1.79**. This method can then lead to the formation of a large number of trisubstituted triazoles **1.80** in a really short period of time.

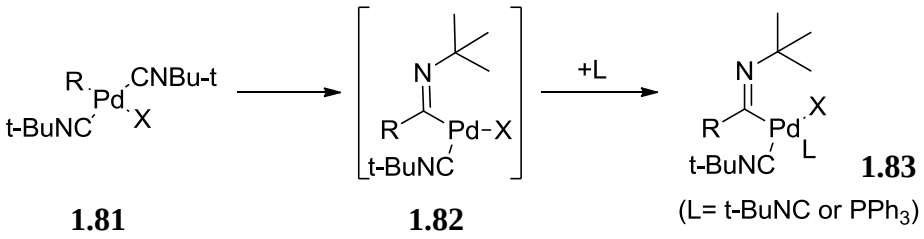


Scheme 16: Synthesis of fully substituted triazoles.

The synthetic power of the palladium-catalyzed carbonylative multi-component reaction does not need to be proven as it fits well the principle of diversity-oriented synthesis of the MCR. However, the main issue with this type of reaction is the use of carbon monoxide, which is a highly toxic gas and sometimes has to be employed under high pressure. One alternative solution is to employ isocyanide instead of carbon monoxide in the carbonylation process.

1.3 Palladium iminoacyl chemistry

In 1969, whereas the insertion of carbon monoxide into a metal-carbon bond[39] was already extensively studied, Otsuka[40] published the first evidence of the insertion of an isocyanide into a Pd-C bond (Scheme 17) and a Ni-C bond. He detected the formation of the palladium iminoacyl complex **1.83** (or palladium imidoyl complex) *in situ*, using NMR analysis. This is the equivalent of the palladium acyl complex, the product of insertion of carbon monoxide into a Pd-carbon bond, and it showed the similar reactivity of carbon monoxide and isocyanides toward metal-carbon bonds.



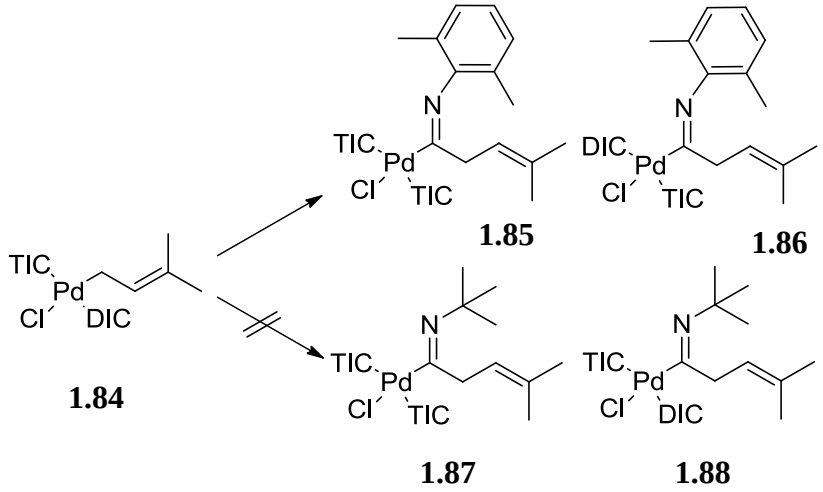
1.81 **1.82**

Scheme 17: Isocyanide insertion in a Pd-C bond as described by Otsuka.

This initial discovery has led to several studies on the formation and utility for synthetic organic chemistry of such complexes. The insertion of isocyanide in alkyl,[41] alkynyl,[42] and aryl palladium bonds is today a well-known process.

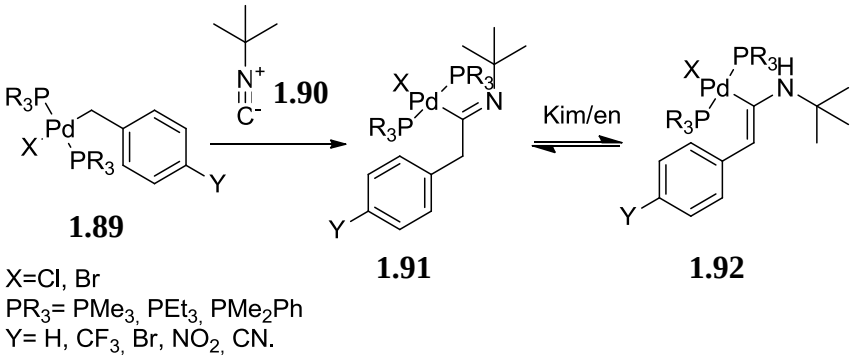
Recently, Vinsentin *et al.* studied the effect of the nature of isocyanides on the process of insertion into a palladium-allyl bond (Scheme 18).[43] They investigated the competitive insertion of 2,6-dimethylphenyl isocyanide (DIC) and *tert*-butyl isocyanide (TIC) in the [Pd (η^3-allyl)] complex. The TIC is supposed to be more electron-donating and more sterically hindered than the DIC. They observed that the heteroleptic complex **1.84** of DIC and TIC with the allylpalladium only undergoes the insertion of the DIC to lead to the complexes **1.85** and **1.86**. The conclusion of this study was that the nature of the isocyanide influences the migratory insertion

process, and that the overall insertion rate is enhanced while increasing the electrophilicity and decreasing the steric hindrance at the isocyanide carbon.



Scheme 18: Competitive insertion of DIC and TIC into a Pd-allyl bond.

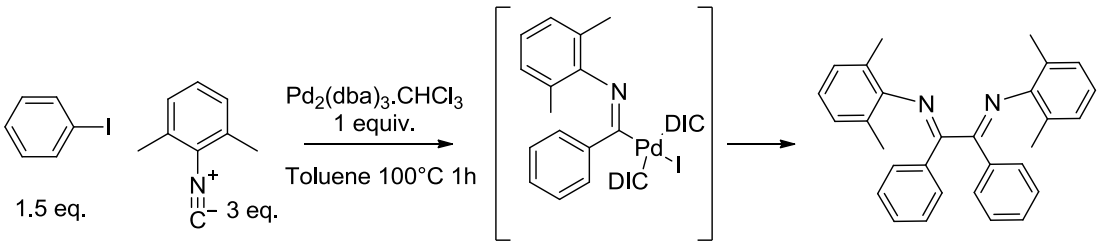
Campora *et al*. showed[44] that the palladium iminoacyl complex can exist in both tautomeric forms as the imine **1.91** and the enamine **1.92** (Scheme 19). They used spectroscopic data of the reaction between benzylpalladium derivatives and *tert*-butyl isocyanide to study this equilibrium and to prove that both forms were existing in the solid state by determining their X-ray crystal structures.



Scheme 19: Imine/enamine tautomeric equilibrium of the Pd-iminoacyl complex.

Although they have the same capacity of insertion into a palladium-carbon bond, carbon monoxide and isocyanides differ in one aspect of this reaction. Indeed, while multiple insertions of carbon monoxide are disfavored, isocyanides can easily undergo the process of consecutive insertions.[45]

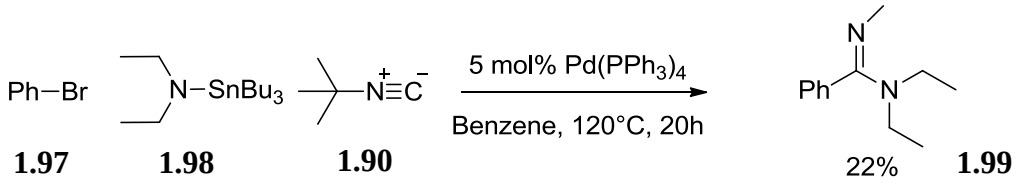
Morishita and Amii[46] discovered that heating a solution of imidoylpalladium complex **1.95** in toluene enables a ligand-coupling reaction to afford α-diimines **1.96** (1,4-diazabutadienes) (Scheme 20). They first generated the diimines from the reaction of an aryl iodide with tri(dibenzylidenacetone)dipalladium ($Pd_2(dba)_3CHCl_3$) and DIC. To elucidate the mechanism of this transformation they isolated the palladium imidoyl complex and heated it in toluene. They then observed the same product in the one-pot reaction. They believed the mechanism to occur in this way: oxidative addition of Pd(0) into the Ph-I bond, insertion of the isocyanide **1.94** in the phenyl palladium complex σ-bond to give the palladium imidoyl complex **1.95**, and then ligand coupling to give the α-diimine **1.96**. However, to obtain the diimine product, a stoichiometric amount of the palladium source has to be employed.



1.93 **1.94** **1.95** **1.96**

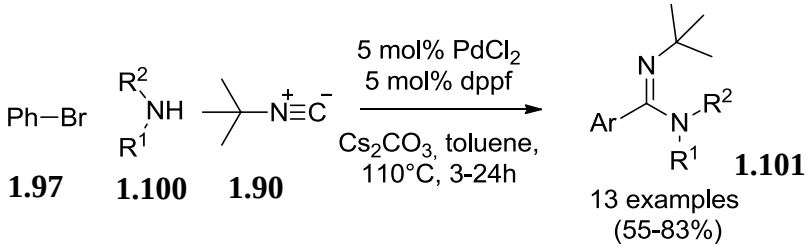
Scheme 20: Dimerisation of the palladium iminoacyl complex **1.95**.

The first example of the use of the Pd-catalyzed isocyanide insertion for the purpose of organic synthesis was described by Kosugi *et al.* in 1986 (Scheme 21).[47] They reported the coupling between bromobenzene **1.97**, *tert*-butylisocyanide **1.90** and tributylstannyl(diethyl)amine **1.98**, to give the amidine product **1.99**. This transformation is probably due to a transmetallation between the stannane and the Pd-iminoacyl complex, followed by the reductive elimination of the palladium to afford the amidine. This could be compared to a Stille reaction mechanism.



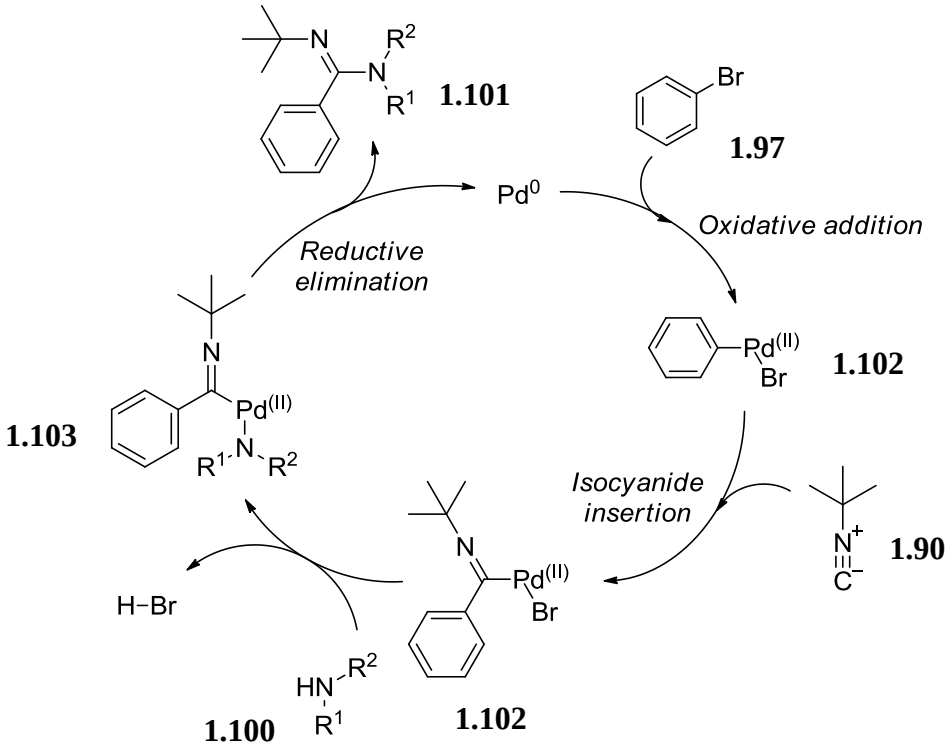
Scheme 21: Kosugi synthesis of amidines.

Fourteen years later, in 2000, Whitby *et al.* proposed[48] an optimized, tin-free procedure for the synthesis of amidines **1.101**, using aryl bromides **1.97**, secondary amines **1.100** and *tert*-butylisocyanide **1.90** (Scheme 22). They optimized the catalytic system and noticed that bidentate phosphine ligands, such as dppf or dppe, were the most efficient.

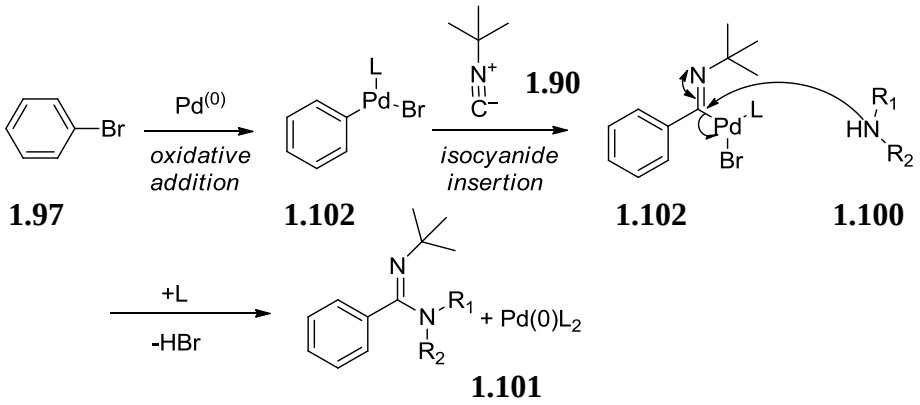


Scheme 22: Whitby's synthesis of amidines[48]

The mechanism of this transformation (as it has not been detailed yet) can be postulated either as a Buchwald-Hartwig mechanism[49] (Scheme 23), where the secondary amine **1.100** acts as a ligand to the palladium and the amidine **1.101** is obtained after the reductive elimination in the palladium iminoacyl complex **1.103**. It could alternatively be considered to go through an addition-elimination process as in the carbonylation with carbon monoxide (Scheme 24).



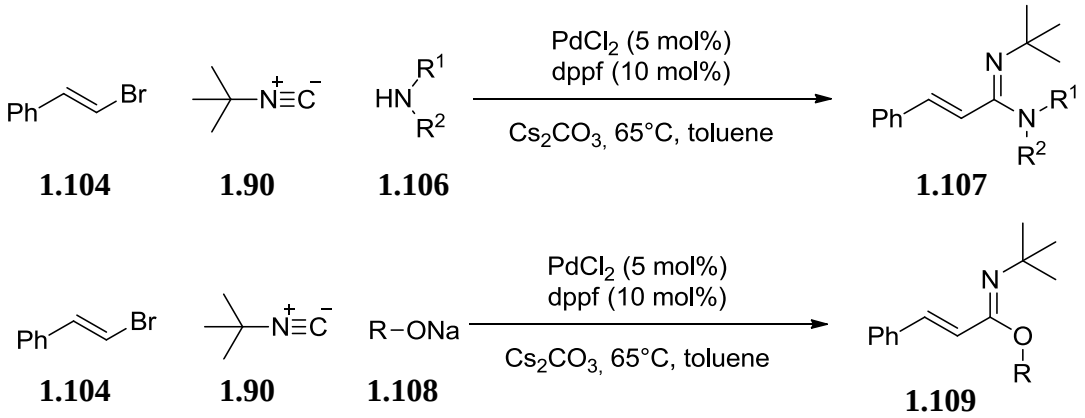
Scheme 23: Buchwald-Hartwig type proposed mechanism



Scheme 24: Addition-elimination type proposed mechanism

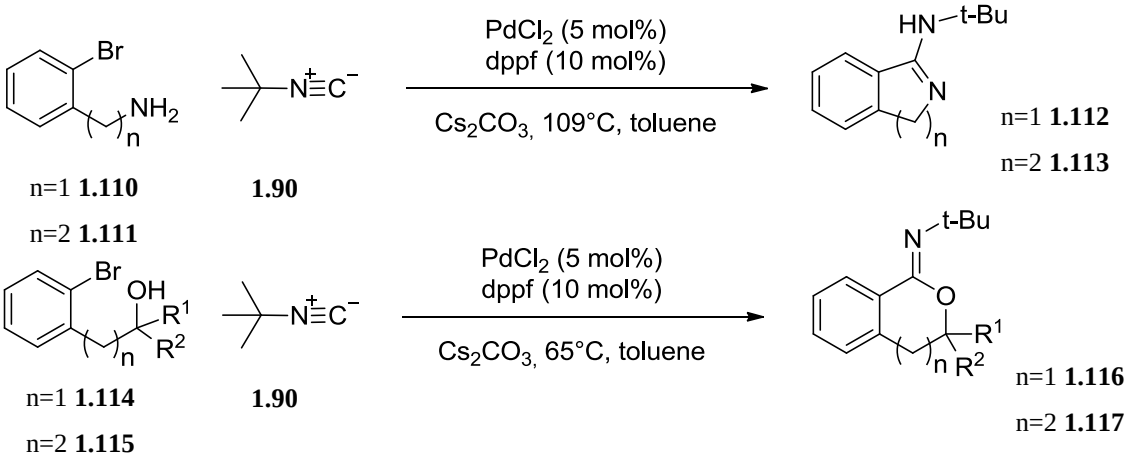
In 2004, Whitby[50] *et al.* also published an extension of this work for the synthesis of α,β-unsaturated amidine **1.107** and imidates **1.108** (Scheme 25). This work showed that their previous method can be applied to alkenyl bromide **1.104** using a secondary amine **1.106** or a sodium alkoxide **1.108**. The interesting point about this three-component reaction is that it is performed at 65°C instead of the 110°C required for the reaction with bromobenzene. The use of sodium alkoxide is also

interesting as it shows that various nucleophiles are able to react with the palladium iminoacyl complex in this method.



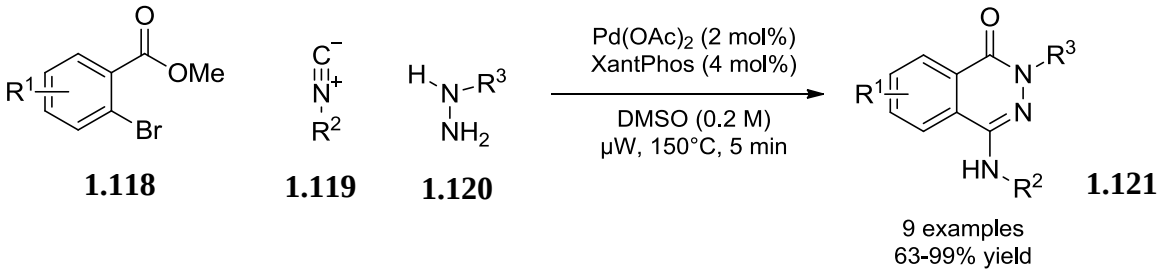
Scheme 25 : Synthesis of α,β-unsaturated amidines and imidates

The same year Whitby *et al.* also published an intramolecular version of the reaction affording cyclic amidines **1.112/1.113** and imidates **1.116/1.117**.[51] For this purpose, they treated aryl bromides containing an amino or alcohol group in the ortho position (Scheme 26). This led to the corresponding cyclised product, but in the case of the amidines, only the endocyclic tautomer **1.112/1.113** was observed. Moreover secondary amines were unreactive under these conditions.



Scheme 26: Synthesis of cyclic amidines and imidates.

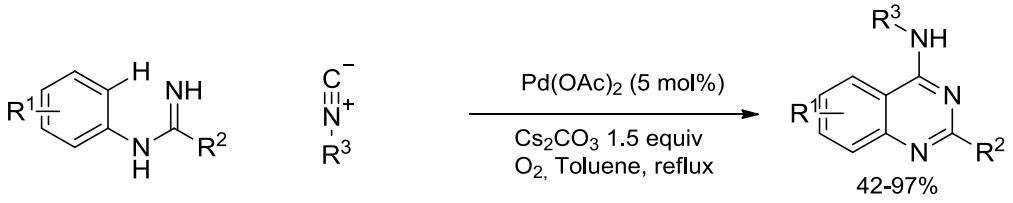
More recently, in 2011, Orru *et al.* have developed a method[52] for the synthesis of aminophthalazinone **1.121** from *o*-bromobenzoates **1.118** and hydrazines **1.120**. The reaction consists here in the insertion of an isocyanide **1.119** catalysed by the palladium, through the formation of a palladium iminoacyl complex, followed by a lactamization to afford the phthlazinone ring.



1.118 **1.119** **1.120** **1.121**

Scheme 27: Orru's synthesis of aminophthlazinone

The same year, Zhu *et al.* described a method[53] of direct synthesis of 4-aminoquinazolines **1.124** from arylamidines **1.122**. This method is based on the palladium catalysed C(sp^2)-H activation of the arylamidines **1.122**, followed by the isocyanide insertion. The reductive elimination of the palladium complex leads to the formation of the corresponding 4-aminoquinazoline **1.124**.



1.122 **1.123** **1.124**

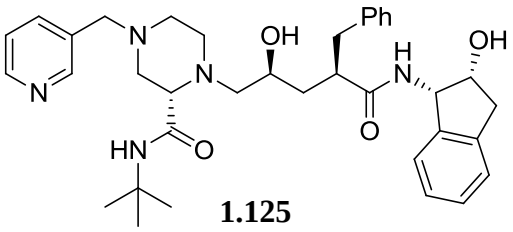
Scheme 28: Zhu's synthesis[53] of 4-aminoquinazolinones via C(sp^2)-H activation

This work summarizes current highlights of the application of Pd-catalyzed isocyanide insertions in MCR for the synthesis of organic molecules and heterocycles. However, as the carbonylative process using carbon monoxide has been proven to be prolific when combined with multi-component reactions, there is still a real interest in developing new methods using isocyanide insertions.

1.4 The project aims

The interest in developing new MCRs has increased in the last two decades with the development of automated methods for the parallel synthesis of organic compounds. The new methods employed in the pharmaceutical industry, like high-throughput screening (HTS), consist in running tests on a large library of compounds.[54] However these libraries have to be generated in the first place, and MCRs are the ideal tool for this.[55]

Indeed, as they present the advantage of affording a product without multiple reactions and purification steps, and as they allow a wide range of products to be formed, this is a fast method for producing several derivatives of one scaffold. There have been many examples of success in discovering biologically active ligands using MCR, either in diversity-[56] or target-oriented[57] approaches. For the same reason, MCR are useful for process chemistry as the final molecule can be obtained in only one step, which simplifies the whole scale-up process. Some commercial drugs are nowadays synthesized *via* MCR, like the HIV protease inhibitor CRIXIVAN® **1.125** (figure 3) using a MCR for the synthesis of piperazine developed within the Merck laboratory.[58]



1.125

Figure 3: HIV protease inhibitor CRIXIVAN®

Developing new MCRs should enhance the scope of product that could be synthesized this way and thereby increase the potential of HTS to find potential biologically active compounds.

As mentioned earlier, the carbon monoxide insertion catalyzed by palladium has been shown to be effective when combined with MCR, but carbon monoxide is a

toxic, colorless and odourless gas. The use of isocyanide seems to be the best replacement for carbon monoxide, and should be as effective. This reason led us to investigate the possibility of developing a new MCR based on palladium-catalyzed isocyanide insertion to produce heterocycles. Indeed heterocycles play a major role in drug discovery as they are present in a large number of bioactive molecules, and examples of commercial drugs containing heterocycles are numerous. The antipsychotic drug Olanzapine **1.126** or the non-steroidal anti-inflammatory Pyroxicam **1.127** (figure 4) are just two amongst hundreds.

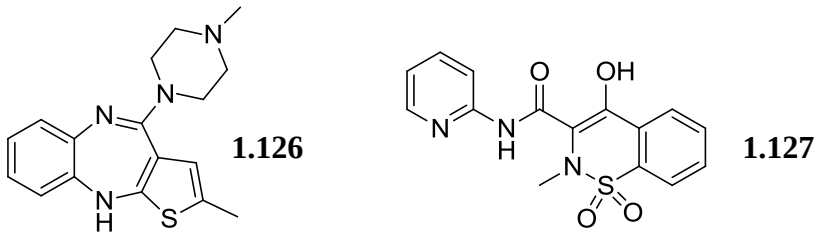
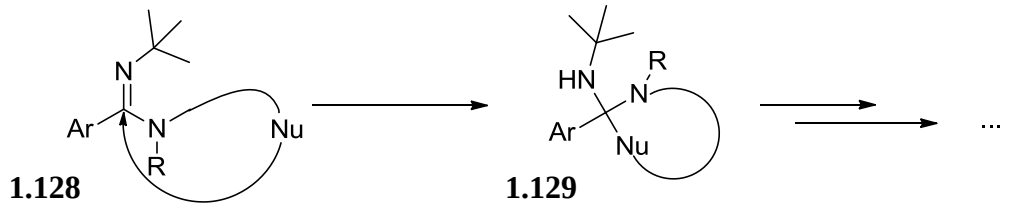


Figure 4 : Olanzapine and Pyroxicam

The basis of the initial investigations was work by Whitby *et al.*[48] on the synthesis of amidines (Scheme 23). It was postulated that this amidine product **1.128** could undergo a nucleophilic attack on an appropriately sited electrophilic carbon. An intramolecular pathway would then hopefully lead to a cyclised product *via* **1.129** (scheme 29).



Scheme 29 : Postulated intramolecular cyclisation of amidine

The goal of the project was then:

-To develop and optimize a palladium-catalyzed reaction of isocyanide insertion to form an amidine with the same type of structure as **1.128** and to find conditions where it could cyclize to give the heteroaromatic compound.

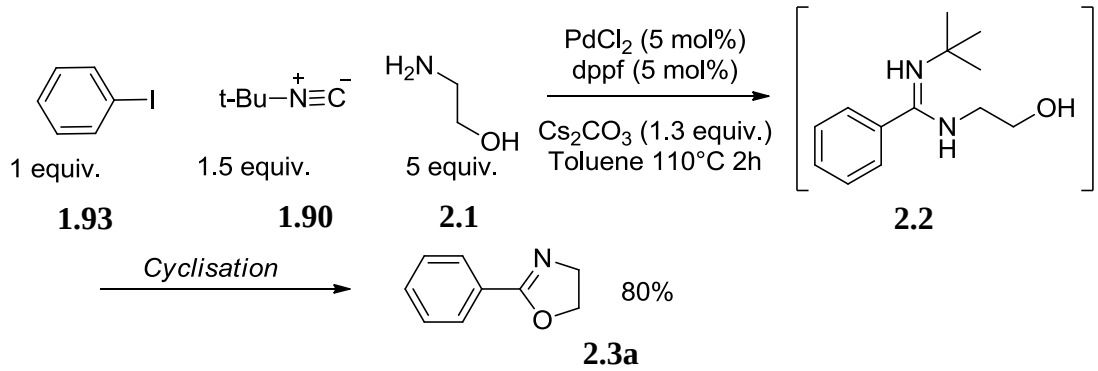
-To apply the method to the synthesis of different sorts of heterocycles (ring size/ type of heteroatoms, …)

-To get a better understanding of the mechanism of this transformations.

2 Results and discussion.

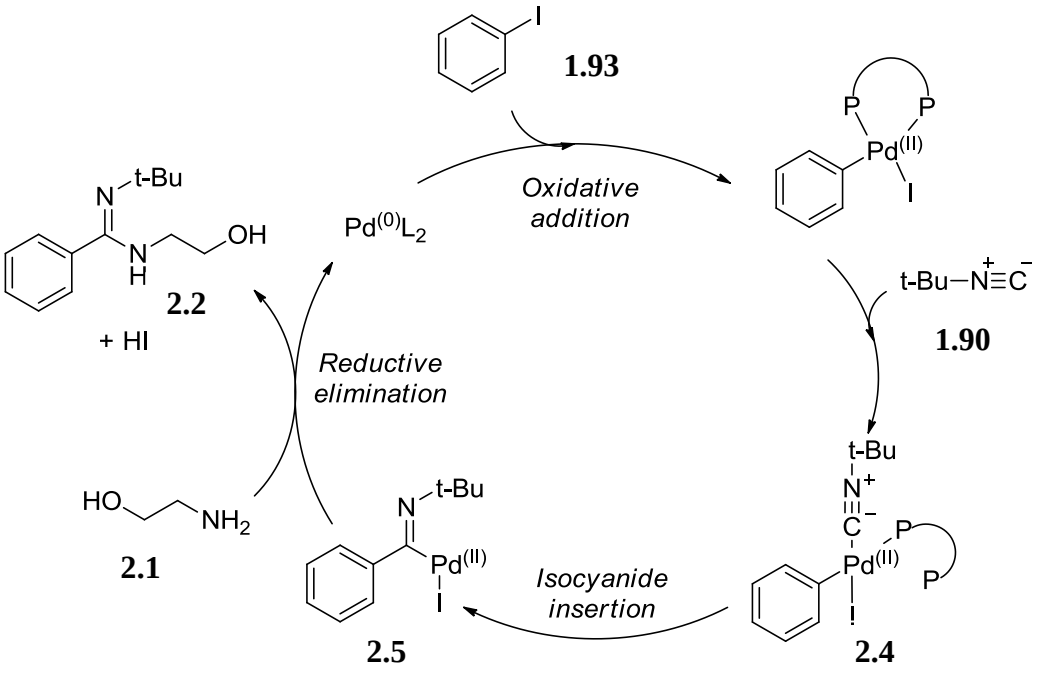
2.1 Synthesis of 2-Aryloxazolines

The investigations were started using conditions similar to those described by Whitby *et al.*[48, 50-51] in their synthesis of amidines and imidates (Scheme 30). The same catalytic system was employed using palladium dichloride as the palladium source and dppf as a ligand Dppf is a bidentate ligand so it was employed in a 1:1 ratio to give [$PdCl_2$(dppf)] which is reduced in situ to the activated $Pd^{(0)}$(dppf) complex. Iodobenzene **1.93** was employed as the aryl halide as it should undergo the oxidative addition of the palladium more easily than bromobenzene. The isocyanide employed was *tert*-butyl isocyanide **1.90** as it proved to be the best from the work of Whitby. The principal difference, and the purpose of the experiment, was the use of ethanolamine **2.1** as the nucleophile source. This should lead to an amidine intermediate **2.2** tethered with an alcohol group. The condensation of this group on the amidine should lead to a cyclic product. The reaction was then set up and refluxed under argon in dry glassware. After disappearance on TLC of the starting iodobenzene **1.93** in the mixture, the reaction mixture was purified and the major product was identified as the 2-phenyloxazoline **2.3a** obtained in a good yield (80%). This work was carried out in our group by Zoe Hamilton for her MChem final year project.[59]

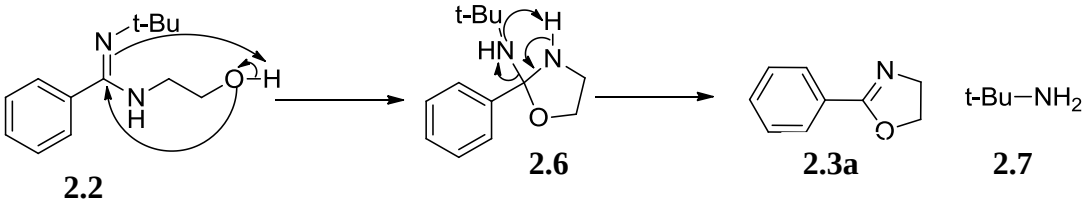


Scheme 30: First assay using ethanolamine.

This very encouraging result confirmed the possibility of synthesizing heterocycles by this way. However, in the cyclisation process, it appeared that the *tert*-butyl amino group was eliminated as *tert*-butylamine **2.7**(Scheme 32). A mechanism could be postulated for this transformation. The formation of the amidine intermediate **2.2** is assumed to go by the same mechanism as the formation of amidines by the Whitby group (Scheme 30). A question remains about the reactivity of the palladium iminoacyl complex with the ethanolamine as it can react in two different ways. Either the ethanolamine **2.1** complexes with the palladium and the reductive elimination of the complex affords the amidine **2.2**, or the palladium iminoacyl complex **2.5** undergoes a nucleophilic attack by the ethanolamine **2.1** on the imine carbon and the palladium is eliminated in an addition-elimination mechanism. The reductive elimination then releases hydriodic acid. The cyclisation step consists in the condensation of the alcohol on the amidine with elimination of *tert*-butylamine **2.7** to afford the 2-phenyloxazoline **2.3a** (Scheme 32).



Scheme 31: Proposed mechanism of the formation of the amidine intermediate.

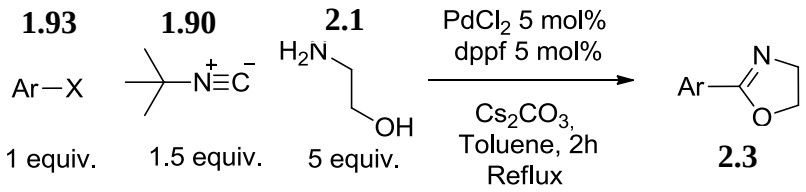


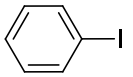
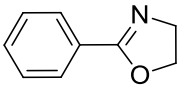
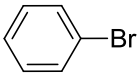
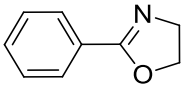
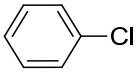
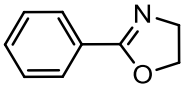
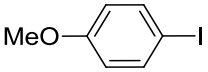
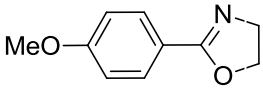
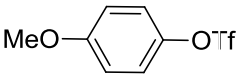
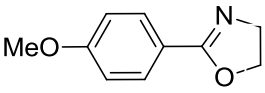
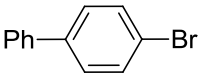
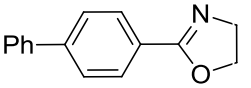
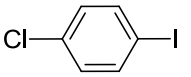
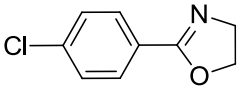
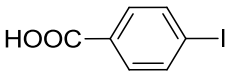
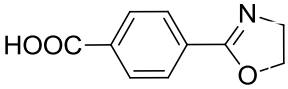
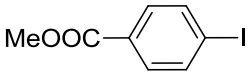
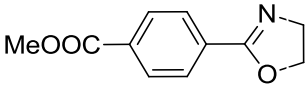
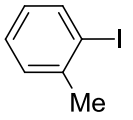
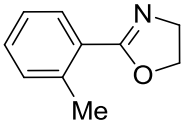
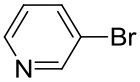
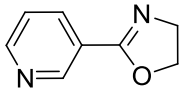
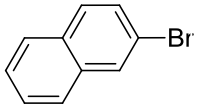
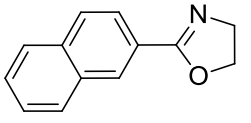
Scheme 32: Mechanism of the cyclisation of the amidine intermediate

After this successful experiment, the investigations were focused on exploring the scope of this reaction. The first aspect to study was the tolerance of the reaction towards various aryl halides. The principal results of this study are shown in Table 1 (p.33).

When bromobenzene **1.97** was employed (entry b), the expected 2-phenyloxazoline **2.3a** was formed as well in a similar yield to iodobenzene **1.93** (entry a). Aryl bromides are then reactive under these conditions. However when chlorobenzene **2.8** was used, no reaction was observed after 2 h of reflux. The aryl chorides seem to be unreactive.

The use of electron-rich aryl groups such as the methoxy group in **2.9** showed a slight drop of yield for the corresponding oxazoline. This is probably due to the capacity of palladium to form a complex with an electron-poor aromatic ring more easily than a electron-rich one, as observed by Norrby.[60] Moreover, when 4-methoxyphenyl trifluoromethanesulfonate **2.10** was employed, a comparable yield was obtained. That suggested that triflates should react as well as iodide or bromide derivatives.



Entry	ArX	Product	Yield (%)
a	 **1.93**	 **2.3a**	80
b	 **1.97**	 **2.3a**	77
c	 **2.8**	 **2.3a**	0
d	 **2.9**	 **2.3d**	69
e	 **2.10**	 **2.3d**	71
f	 **2.11**	 **2.3f**	81
g	 **2.12**	 **2.3g**	72
h	 **2.13**	 **2.3h**	26
i	 **2.14**	 **2.3i**	0
j	 **2.15**	 **2.3j**	69[(a)]
k	 **2.16**	 **2.3k**	93
l	 **2.17**	 **2.3l**	88

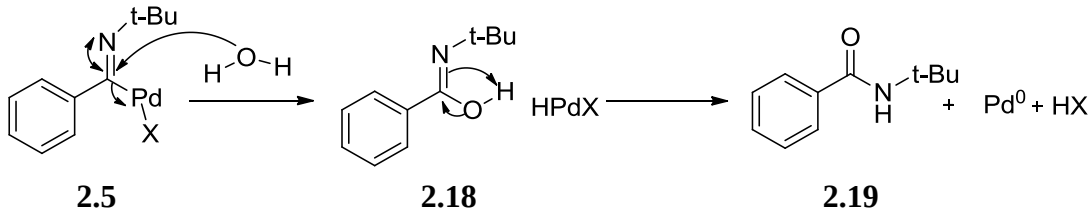
(a) Reaction time increased to 18h

Table 1 : Variation of the Aryl halide.

When electron-poor aryl halides were employed, various results were observed. Indeed, when the reaction was performed with 4-chloro-iodobenzene **2.12** a good yield was obtained. However, when an ester group was employed, such as methyl 4-iodobenzoate **2.14**, no oxazoline product was observed. This could be due to side-reactions occurring between the substrates, even without the influence of the palladium catalyst. However, no other products have been isolated to clarify what kind of side-reactions were happening. The reaction with the carboxylic acid **2.13** was successful to an extent where the oxazoline product **2.3h** has been isolated, albeit in low yield. In the case of the 3-bromopyridine **2.16**, the oxazoline **2.3k** was obtained in an excellent yield. This result shows that electron- poor aryl bromides can react efficiently under these conditions. In the case of the ester **2.14** or the carboxylic acid **2.13**, the poor yield should be due to the reactivity of these groups with the other starting materials.

The oxazoline products **2.3f** and **2.3l** have been obtained in good yield when 4-bromo-1,1'-biphenyl **2.11** or 2-bromonaphthalene **2.17** were employed. This suggests that other aromatic compounds than simple halobenzenes are suitable to these reaction conditions. Nevertheless when 2-iodotoluene **2.15** was reacted for 2 hours under the same conditions, the corresponding oxazoline **2.3j** was not isolated. A mixture of this oxazoline and what could be the uncyclised imidate was observed by NMR. The reaction was then performed once again but the reaction time was extended to 18h, and in this case, a good yield was obtained for the expected oxazoline product **2.3j**. The use of *ortho*-substituted aryl halides might be challenging then, and appeared to need a longer reaction time. This could be due to the steric hindrance of the *ortho* group that might slow down the insertion and the cyclisation step.

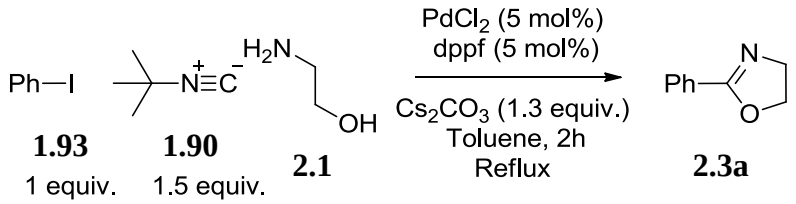
It was also observed that the reaction should be carried out under dry conditions to prevent hydrolysis of the reaction intermediate (Scheme 33). Indeed, the palladium iminoacyl complex **2.5** can be hydrolyzed to give the corresponding amide **2.19**.[43] This product has been isolated in some cases where the glassware or the reactants were not dry enough.



2.5 **2.18** **2.19**

Scheme 33: Hydrolysis of the $Pd^{(II)}$-iminoacyl complex **2.5**.

The potential scope of aryl halides for this reaction was clearer with these results. However, the reaction conditions employed needed 5 equivalents of the ethanolamine **2.1** (relative to the quantity of aryl halide involved). The impact of decreasing this amount of ethanolamine while keeping the other conditions the same was studied. The reaction was then performed with the conditions of the first experiment (Scheme 30) with iodobenzene **1.93**, *tert*-butylisocyanide **1.90** and ethanolamine **2.1**, but using varying quantities of this last reagent. The outcomes of these experiments are summarized in Table 2.

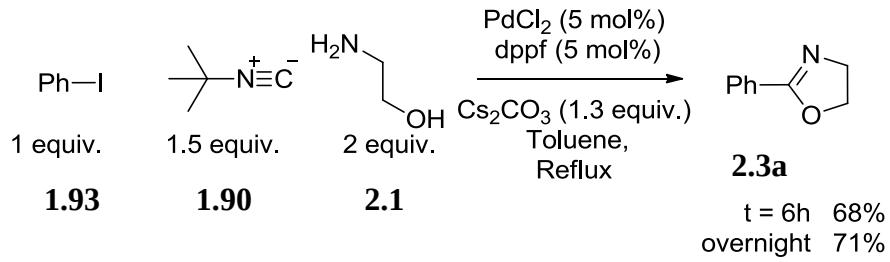


Ethanolamine **2.1**[(a)]	Yield in **2.3a**(%)
5 equiv.	80
3 equiv.	68
2 equiv.	56

(a) Relative to 1equiv. of iodobenzene

Table 2: Influence of the quantity of ethanolamine

When the amount of ethanolamine **2.1** was decreased to 2 equivalents, a yield of 56% of the ethanolamine was obtained compared to the 80% when 5 equivalents were employed. When the reaction was performed with 3 equivalents a better yield was obtained (68%) but it was still lower than the first assay with 5 equivalents of ethanolamine. It suggests that the large excess of ethanolamine **2.1** is needed. One possible explanation can be that it needs to chelate the palladium complex **2.5** in order to react with it and prevent its reaction with other substrates present in the reaction mixture. It could also be due to a kinetic aspect of the reaction. In this case, increasing the reaction time could improve the yield using a lower amount of ethanolamine **2.1**. To test this, reactions employing only two equivalents of ethanolamine **2.1** were performed with an extended reaction time (Scheme 34). One of the reactions was left overnight and the other one was run for 6 hours.



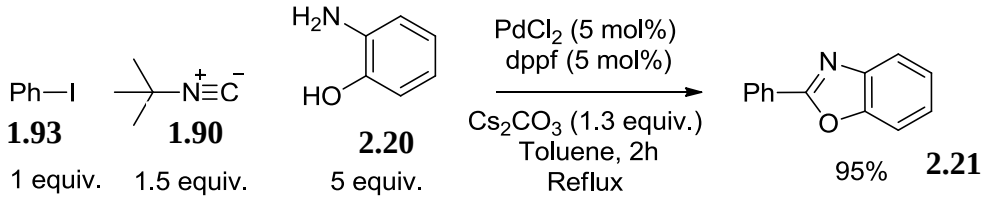
Scheme 34 : Influence of reaction time on the synthesis of 2-phenyloxazoline **2.3a**

The reaction which was run for 6 hours showed a significant increase of the yield (68%) of 2-phenyloxazoline **2.3a** when compared to the reaction of 2 hours displayed in Table 2 (56% yield). The overnight reaction also showed an improved yield (71%) which is comparable to the 6 hour's reaction but still lower than the reaction employing five equivalents of ethanolamine **2.1**. Therefore, increasing the reaction time can compensate for using a lower amount of dinucleophilic starting material with only a slight drop in yield.

These reaction conditions have proved to be suitable for the synthesis of oxazolines in good yields and they can be applied to a wide range of aryl halides. The principal limit seemed to be due to the presence of a substituent on the aryl group which impedes nucleophilic attacks, and the side-reactions it can provoke. The possibility of varying the two different nucleophilic centers, i.e. to use nucleophiles other than ethanolamine seemed to be the most straightforward line of investigation.

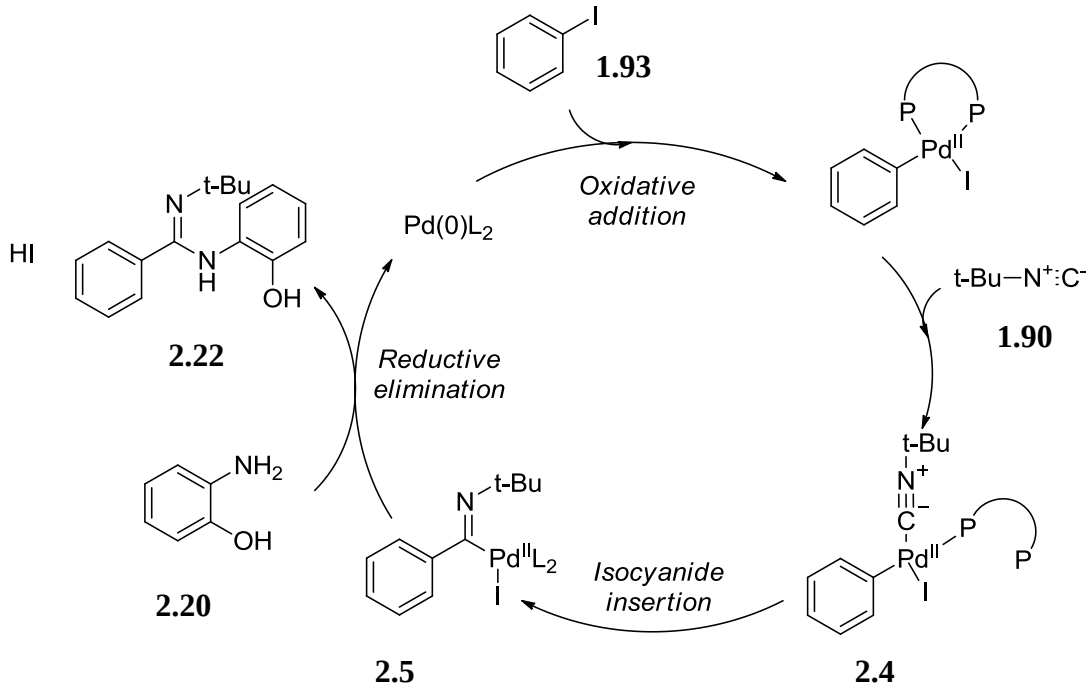
2.2 Synthesis of 2-Arylbenzoxazoles

To start our investigation of the application of the method to the synthesis of benzoxazoles, ethanolamine **2.1** was now replaced in the reaction by 2-aminophenol **2.20** (Scheme 35). The exact same conditions were employed, the same catalytic system [$PdCl_2$(dppf)], 5 equivalents of 2-aminophenol **2.20**, in toluene and the reaction was refluxed for 2 hours. The aryl halide employed here was iodobenzene **1.93**



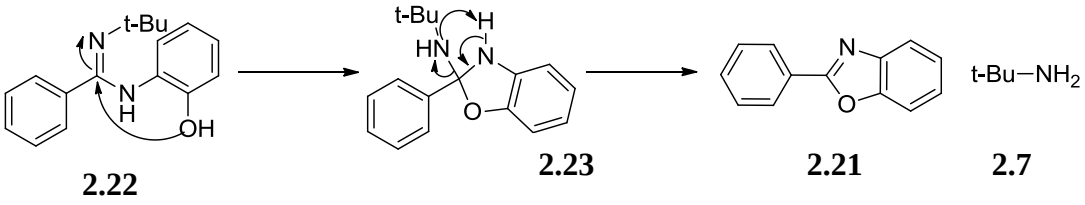
Scheme 35: First successful attempt at synthesis of 2-phenylbenzoxazole **2.21**.

The first attempt at the reaction gave satisfying results as 2-phenylbenzoxazole **2.21** was isolated in an excellent yield, 95%. The conditions employed for the synthesis of oxazoline **2.3** were used for the synthesis of benzoxazole **2.21**. It is likely that the reaction should go through the same mechanism (Scheme 36).



Scheme 36: Proposed catalytic cycle.

The cyclisation step could be enhanced by the rigid structure of the 2-aminophenol **2.20** (Scheme 37). Indeed the spacial proximity between the hydroxyl group and the amidine in the intermediate **2.22** should favour the reaction between these two groups compared to the intermediate in the synthesis of oxazolines.

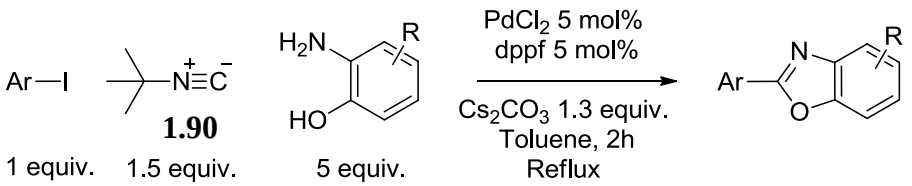


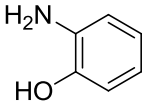
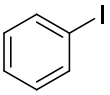
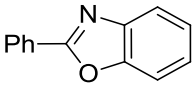
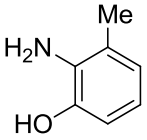
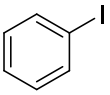
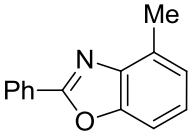
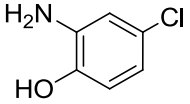
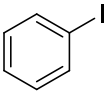
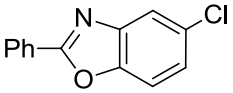
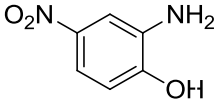
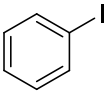
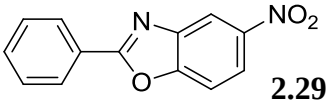
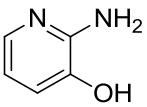
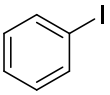
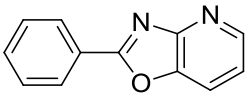
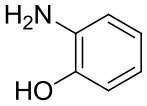
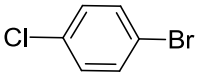
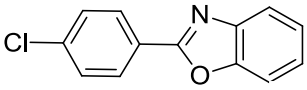
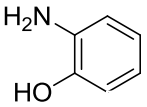
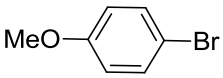
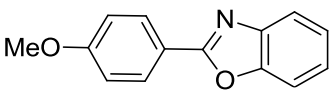
2.22 **2.23** **2.21** **2.7**

Scheme 37 Cyclisation of **2.22**

The influence of the nature of the aminophenol was investigated (Table 3). The effect of having a substituent in the 3-position of the aminophenol was studied with 2-amino-3-methylphenol **2.24**. A similar yield was obtained for the benzoxazole product **2.25**, so the substituent in the 3 position does not seem to have a negative impact on the reaction. When 2-amino-4-chlorophenol **2.26** was employed, the benzoxazole product **2.27** was also obtained in an excellent yield.

Aryl halides different than iodobenzene **1.93** were also employed such as 1-bromo-4-chlorobenzene **2.32** and 1-bromo-4-methoxybenzene **2.34,** which respectively gave 2-(4-chlorophenyl)benzoxazole **2.33** and 2-(4-methoxyphenyl)benzoxazole **2.35** in excellent yields as well. Therefore, the influence of the nature of the aryl halide on the reaction must be similar to the one observed in the synthesis of oxazoline (Table 1).



Aminophenol	Aryl Halide	Product	Yield (%)
 **2.20**	 **1.93**	 **2.21**	95
 **2.24**	 **1.93**	 **2.25**	96
 **2.26**	 **1.93**	 **2.27**	98
 **2.28**	 **1.93**	 **2.29**	0
 **2.30**	 **1.93**	 **2.31**	0
 **2.20**	 **2.32**	 **2.33**	92
 **2.20**	 **2.34**	 **2.35**	99

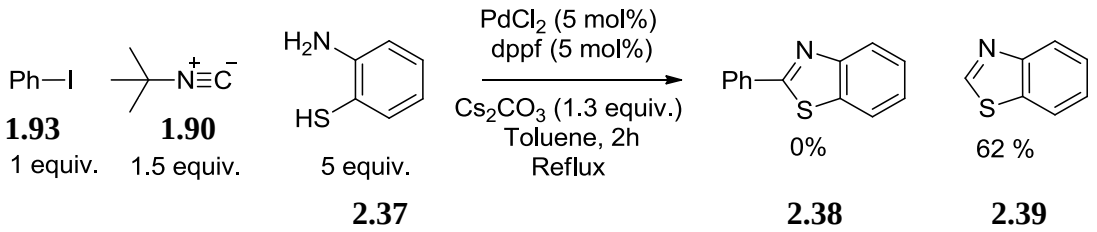
Tables 3 : synthesis of 2-aryl benzoxazoles

However, this reaction was unsuccessful when 2-amino-4-nitrophenol **2.28** or 2-aminopyridin-3-ol **2.30** were employed. This might be due to a lack of nucleophilicity of the amino group. The presence of the nitro group in the *meta* position with the amino group should impact the electron density around the nitrogen and therefore its nucleophilic power. Something similar might be occurring with the aminopyridine substrate **2.30**. The rate of the nucleophilic addition of the amino-alcohol on the palladium iminoacyl complex should drop if this hypothesis is true and this would impact the whole transformation.

The application of this method for the synthesis of benzoxazoles was then successful in most of the cases studied, giving excellent yields. However there are still some problematic substrates. The possible application of this method to the synthesis of benzothiazoles was then studied.

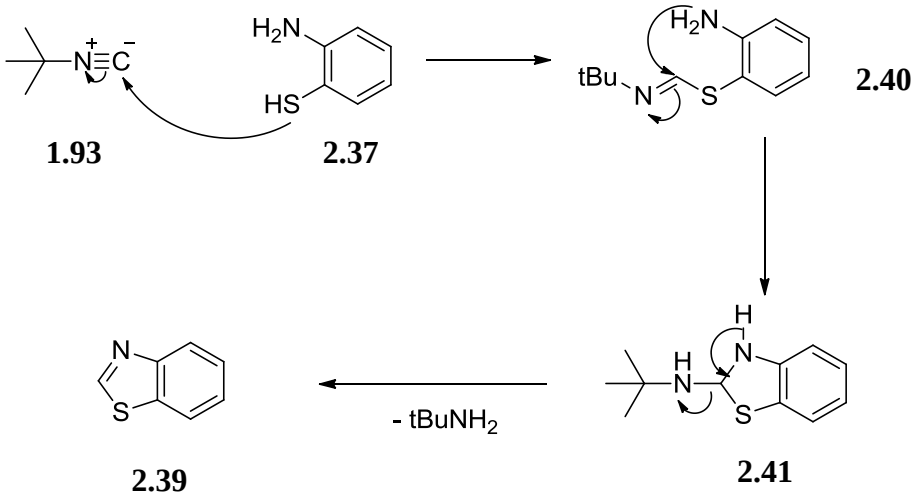
2.3 Synthesis of 2-Arylbenzothiazoles

To begin our investigation of applying the reaction conditions to the synthesis of benzothiazoles, the same conditions to those employed for the synthesis of benzoxazoles were used on 2-aminobenzenethiol **2.37** (Scheme 38). The reaction was performed but surprisingly did not lead to any formation of the expected 2-phenylbenzothiazole **2.38**, but to the unsubstituted benzothiazole **2.39** with a yield of 62% (based on the isocyanide **1.90**).



Scheme 38: First attempt at the synthesis of 2-phenylbenzothiazole

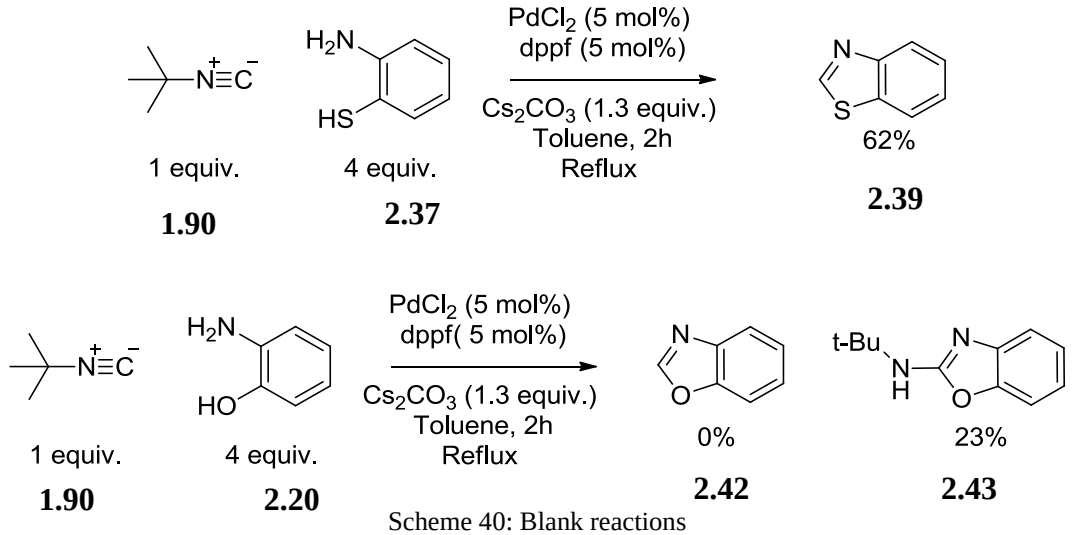
This result was unexpected and was in contradiction with our postulated mechanism for the synthesis of benzoxazoles. A mechanism for this transformation can be postulated (Scheme 39) where the isocyanide **1.93** undergo a nucleophilic attack of the thiol group of the aminothiophenol **2.37**. Then the cyclisation of the product **2.40** occurs with a condensation of the amine group on the imidothioate group to form the cyclic product **2.41**. The final benzothiazole **2.39** is then obtained with the elimination of *tert*-butylamine.



1.93 **2.37** **2.40** **2.41** **2.39**

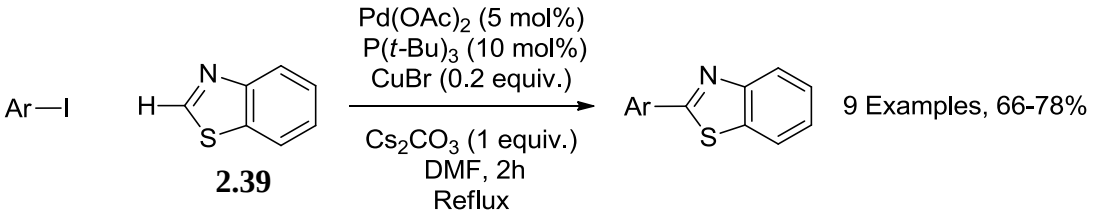
Scheme 39: Proposed mechanism accounting for the formation of the unsubstituted benzothiazole..

To gain a better understanding of the difference of reactivity between aminophenols and aminothiophenols, "blank" reactions were performed, using 2-aminophenol **2.20** and 2-aminothiophenol **2.37** without adding any aryl halide to the reaction mixture (Scheme 40). As the aryl halide should not be involved in the transformation leading to the unsubstituted benzothiazole **2.39**, the blank reaction should result in its formation. Indeed the same benzothiazole **2.39** was isolated from the blank reaction. However, the blank reaction with 2-aminophenol **2.20** did not afford the unsubstitued benzoxazole **2.42** but the *N*-(tert-butyl)benzoxazol-2-amine **2.43**. This suggests that the two reactions with the iodoarene **1.93** do not use the same type mechanism. This difference of reactivity between the aminophenol **2.20** and the aminothiophenol **2.37** must be due to the sulfur and its reactivity toward the isocyanide **1.90** and the palladium.



Scheme 40: Blank reactions

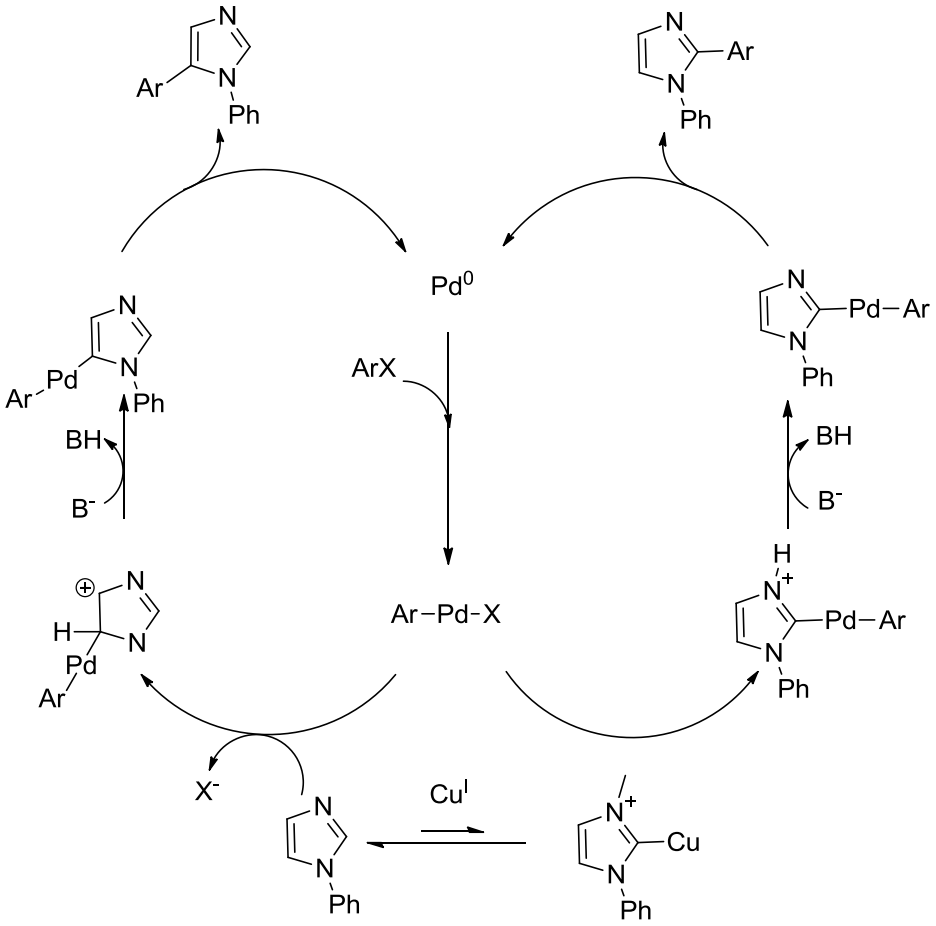
As the absence of the aryl halide does not seem to affect the formation of the benzothiazole **2.39**, we investigated the possibility of using it to complete the synthesis of the 2-phenylbenzothiazole **2.38**. There are precedents in the literature for metal-catalysed arylation of benzothiazole **2.39**.[61] Most of them use a copper species as a co-catalyst. The work of Alagille *et al.*[62] caught our attention as it describes a palladium/copper catalyic system for the direct arylation of benzothiazole **2.39** using a palladium acetate and tri-*tert*-butylphosphine catalytic system (Scheme 41), which is close to the palladium dichloride/dppf system employed in the investigated reaction.



Scheme 41: Alagille's synthesis of 2-arylbenzothiazoles.

Moreover, the direct arylation of heterocycles such as imidazoles and thiazoles derivatives using co-catalytic system with palladium and copper has been investigated several times in the past. The first to published some work on this sort

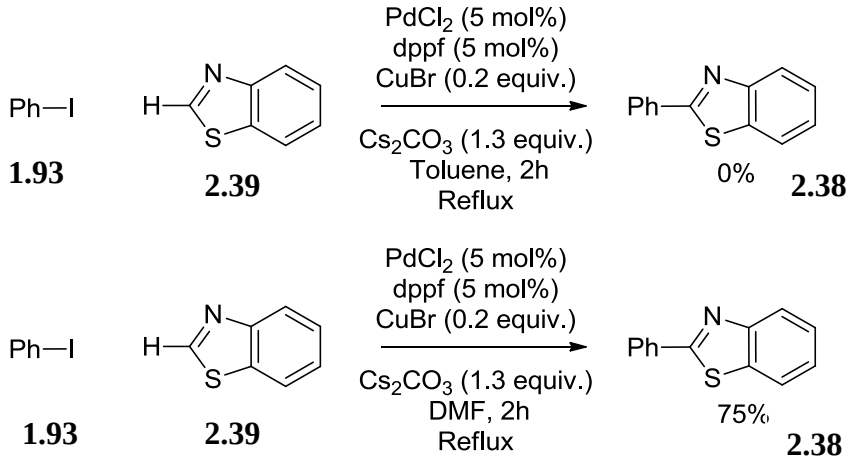
of reaction was Millson[63] in 1974. The group of Bellina and Rossi have published many results[64] relative to this type of transformations. They studied the regioselective arylation of imidazoles at the C2 and C5 positions and showed that the C2 arylation mechanism was going through an organocopper intermediate (Scheme 42). They also applied this same method for the arylation of thiazoles.



Scheme 42: Proposed mechanism for arylation of C2 and C5-arylation of imidazole.

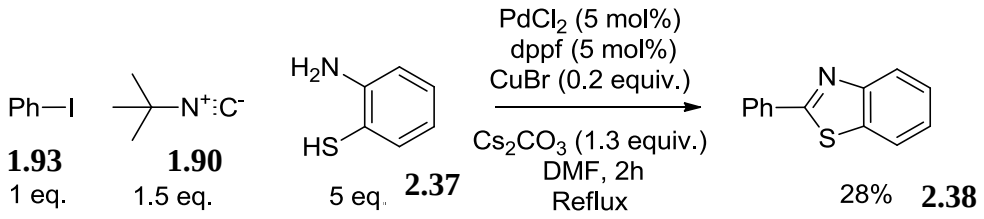
Fairlamb and co-worker also did an extensive reviews of direct C-H/C-X coupling methodologies using palladium-copper co-catalytic systems.[65] This gave good hopes in the possibility of employing such a system in the synthesis of benzothiazoles. We envisaged the possibility of synthesizing the 2-arylbenzothiazole **2.38** with our initial conditions but adding copper bromide as a co-catalyst. For this purpose, the reaction of iodobenzene **1.93** with benzothiazole **2.39** with an additional 0.2 equiv. of copper bromide was performed. However no formation of the expected 2-

phenylbenzothiazole **2.38** was observed. The solvent, toluene, was suspected to be the reason for this result, as DMF, a solvent with a much higher boiling point, was employed in Alagille's procedure.[62] The temperature, the solvent polarity and the solubility of cesium carbonate might be factors in the activation of the benzothiazole **2.39** by the copper. The same reaction was performed in DMF, and gave encouraging results as a good yield of the 2-phenylbenzothiazole **2.34** was isolated (Scheme 43).



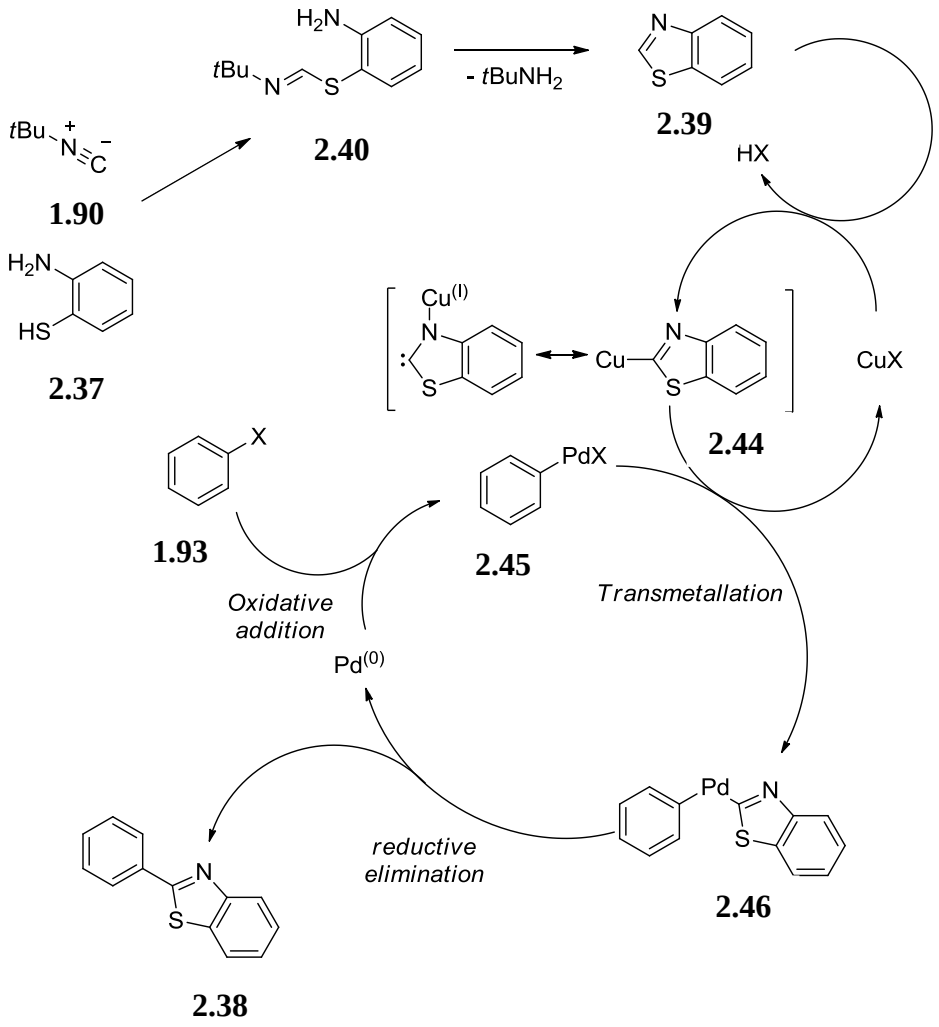
Scheme 43: Influence of the solvent type.

This showed the possibility of coupling aryl halides with benzothiazole **2.39** using our initial conditions with additional copper salts. Therefore, the benzothiazole **2.39** formed during the reaction between isocyanide **1.90** and 2-aminothiophenol **2.37** should react with the iodobenzene **1.93** in the presence of the copper co-catalyst CuBr, if performed in DMF at a higher temperature (Scheme 44). This reaction was successful, and even if the 2-phenylbenzothiazole **2.38** was obtained in a low yield, it validated our hypothesis.



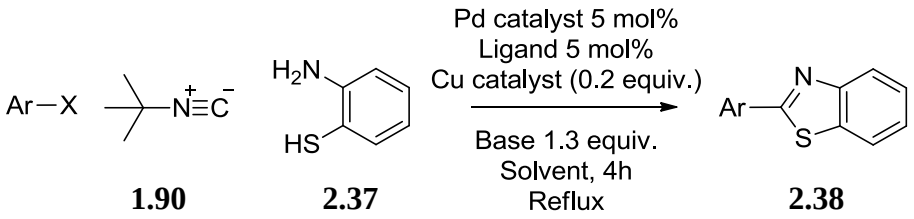
Scheme 44: First one-pot synthesis of 2-phenylbenzothiazole

From this result, a synthetic sequence can be postulated (Scheme 45). This sequence starts with the formation of the benzothiazole **2.39** from the aminothiophenol **2.37** and the isocyanide **1.90**. This benzothiazole is activated by the copper catalyst which activates the C-H bond in the 2-position, to give an organocopper compound **2.44**, whereas the iodobenzene **1.93** undergoes an oxidative addition by the $Pd^{(0)}$ species. Then a transmetallation occurs between the 2 organometallic compounds **2.44** and **2.45** to give a palladium complex **2.46** and regenerate the copper catalyst as copper iodide. The reductive elimination of the palladium complex **2.46** afforded the 2 phenylbenzothiazole **2.38** and regenerated the $Pd^{(0)}$.



Scheme 45: Postulated catalytic mechanism of the formation of 2-phenylbenzothiazole.

This encouraging result left the possibility of optimizing this reaction to improve the yield of the benzothiazole product **2.38**. At first, it was observed that a reaction time of 2 hours was not enough to consume all the starting iodobenzene **1.93**, however increasing it to 4 hours appeared to be sufficient. Several factors of the reaction were then investigated and the corresponding experiments are shown in Table 4.



1.90 **2.37** **2.38**

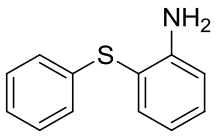
Entry	ArX	Eq. of **1.90**	Eq of **2.37**	Pd catalyst	Ligand	Cu catalyst	Base	Solvent	Yield (%)
a	PhI	1.5	5	$PdCl_2$	dppf	CuBr	Cs_2CO_3	DMF	28
b	"	2.5	2.5	"	"	"	"	"	33
c	"	"	"	"	P(*t*-Bu)$_3$ 10 mol%	"	"	"	5
d	"	"	"	$Pd(OAc)_2$	dppf	"	"	"	36
e	"	"	"	"	"	CuI	"	"	40
f	PhBr	"	"	"	"	"	"	"	38
g	PhI	"	"	"	"	"	2,6-lutidine	"	38
h	"	"	"	"	"	"	Et_3N	"	37
i	"	"	"	"	"	"	K_3PO_4	"	39
j	"	"	"	"	"	"	Cs_2CO_3	DMAc	25
k	"	"	"	"	"	CuI 5 mol%	"	DMF	59

(") :Same as above

Table 4: Optimisation of 2-phenylbenzothiazole synthesis.

The first aspect investigated was the quantity of isocyanide **1.90** and aminothiophenol **2.37** involved in the reaction. As the unsubstituted benzothiazole **2.39** was obtained in good yield from a equimolar mixture of isocyanide **1.90** and aminothiophenol **2.37**, these conditions were tried in the complete reaction, entry b. The two components were introduced in the same quantity but still in excess compared to the iodobenzene **1.93**. The yield was better under these conditions, which is probably due to the fact that the benzothiazole **2.39** is formed in higher quantity. When the ligand was changed to tri-*tert*-butylphosphine (entry c), which was employed by Alagille in his procedure, a substantial decrease in yield was observed. This could be due to the monodentate ligand, and that should impact the rate of the formation of the benzothiazole **2.39**, or the reductive elimination step, which is favoured by the use of bidentate ligand. The palladium catalyst source was changed to palladium acetate (entry d) a slight improvement of the final yield was observed. In addition, the reaction appeared to run more cleanly and to be easier to purify than in the case where palladium dichloride was employed. The substitution of copper bromide by copper iodide (entry e), as the copper catalyst, was found to be beneficial to the final yield.

At this stage it was realised that the final mixture contained, besides the 2-phenylbenzothiazole **2.38**, two other products in significant quantities. These products were isolated, and identified as the unsubstituted benzothiazole **2.39** and as the 2-(phenylthio)aniline **2.47** (figure 8).

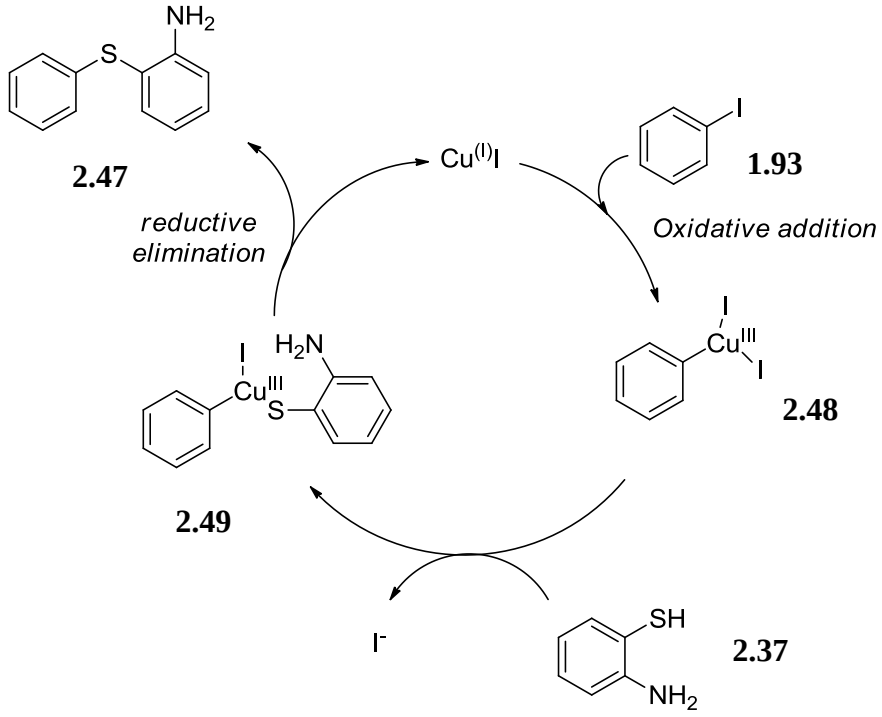


2.47

Figure 8: 2-(phenylthio)aniline

This by-product can arise through an Ullmann type coupling occurring between the aminothiophenol **2.37** and the iodobenzene **1.93**,[66] catalyzed by the copper (Scheme 46). Indeed, in 1904 Ullmann described a procedure[67] for the coupling of aryl halide with phenol, thiophenols or aniline catalyzed by copper powder or salts. This

transformation has been widely studied and optimised since.[66, 68] However, in this case iodobenzene **1.93**, the limiting reactant of the reaction, is consumed by this side reaction and therefore cannot react as expected with the *tert*-butylisocyanide. Moreover, around 40% yield, relatively to iodobenzene **1.93**, of this product **2.47** has been observed. This means than 40% of the sta rting iodobenzene **1.93** is unable to react in the coupling with the benzothiazole intermediate **2.39**. This was the main obstacle on the way to obtaining a good yield of 2-phenylbenzothiazole **2.38**. Therefore, the optimisation of this reaction should focus on preventing this Ullmann-type side reaction to occur.



Scheme 46: Mechanism of the Ullmann reaction leading to **2.47**

The use of bromobenzene **1.97** (entry f), which is supposed to be less reactive toward the Ullmann coupling than the iodobenzene **1.93**,[66] was investigated, but no significant difference was observed. Some studies about the copper-catalysed biaryl ether synthesis mention the fact that the nature of the base involved can have an impact on the rate of the transformation. This possibility was studied with the use of organic bases such the 2,6-lutidine (entry g) and triethylamine (entry h) or another inorganic base, potassium phosphate (entry i). However, a similar yield of benzothiazole **2.38** was observed in every cases, which was not an improvement,

and it did not seem to have an impact on the formation of the 2-(phenylthio)aniline **2.47**.

For all these reactions, DMF was employed as a solvent, and the reaction was refluxed for 4 hours. However, DMF is known to decompose when reaching its boiling point. It is supposed to decompose to dimethylamine and carbon monoxide.[69] As this might be an issue, the replacement of this solvent by di-methylacetamide (DMAc), which is more stable, was studied (entry j). However it proved to be inefficient as the yield of benzothiazole **2.38** decreased.

As no improvement was obtained with the preceding investigations, one of the other obvious possibilities to look at was decreasing the amount of the copper catalyst involved. This should slow the rate of the Ullmann-type side reaction. The quantity of copper iodide involved was then decreased (entry k). This led to a significant improvement as a yield of 59% was obtained for the benzothiazole, which is a good yield for the multi-component reaction.

2.4 Conclusion and future work.

A rapid and efficient synthesis of 2-aryloxazolines (**2.3a-l**) has been developed through a palladium-catalyzed multi-component reaction involving the process of isocyanide insertion. This reaction was suitable for a wide range of starting materials, with the exception of the presence of an ester substituent on the aryl halide. Besides this example, electron-rich and electron-poor and sterically hindered aryl halides proved to be reactive.

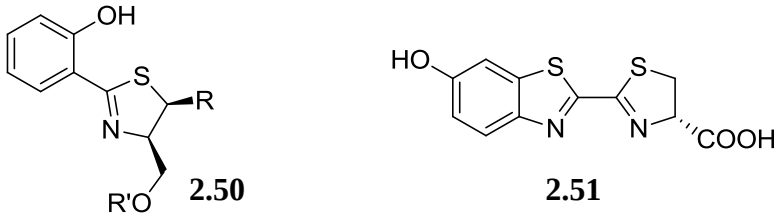
When applied to the synthesis of 2-arylbenzoxazoles, this procedure was shown to be very efficient, as excellent yields were obtained. However a few number of substrate appeared to be unreactive. This is probably due to the electronic effect of the other substituent on the aminophenol ring and could be an area to investigate to

extend the potential scope of the reaction. A rational mechanism can be postulated, however it requires more evidence. Computational studies on this topic are ongoing and might help to confirm the hypothetical mechanism.

The synthesis of 2-arylbenzothiazoles is still at an early stage of development. An efficient procedure affording the 2-phenylbenzothiazole **2.29** has been developed, but the potential scope of the reaction, its tolerance toward the nature of the starting aryl halides and aminothiophenols still has to be investigated. Moreover, there is still the possibility of improving the final yield while trying to limit the formation of the biaryl thioether side product **2.47**. The mechanism of this transformation still remains unknown, especially for the formation of the benzothiazole **2.38**. Computational investigations on this transformation are also ongoing.

Future work:

It might be interesting to investigate the potential use of these methodologies in the synthesis of relevant bioactive complex molecules or natural products, such as the Pulicatins[70] **2.50**, or Luciferin[71] **2.51**.



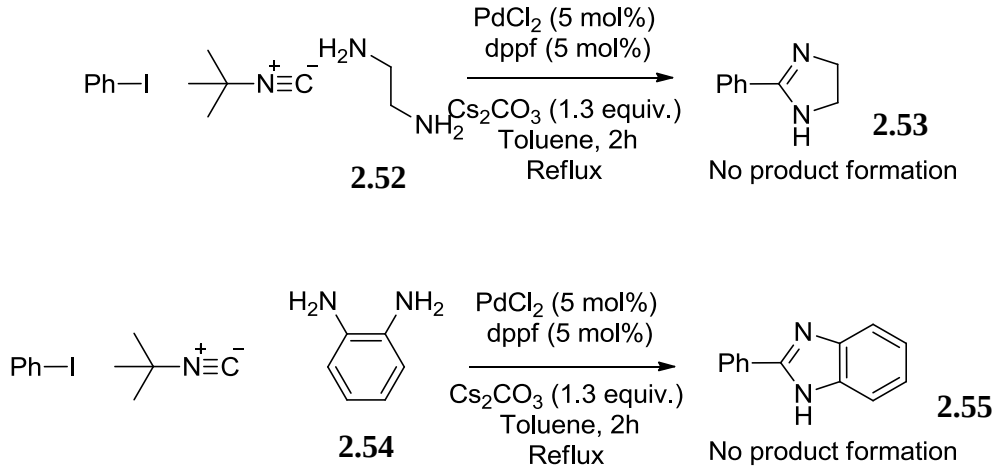
2.50 **2.51**

Figure 9: Pulicatin and Luciferin

Moreover, the application of this method to a product such as the Pulicatins family would study the behaviour of the reaction toward enantiopure starting materials, and therefore study its potential use in asymmetric synthesis.

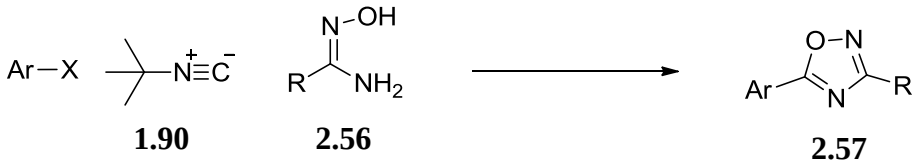
Another line of investigation can be studying the use of other types of di-nucleophilic starting materials to lead to other heterocycles. One of the most

straightforward substrates to employ would be the diamines, such as ethane-1,2-diamine **2.52** or *o*-phenylenediamine **2.54**, to lead to the formation of imidazolines **2.53** or benzimidazoles **2.55** (Scheme 47). However this might need further investigations and some adjustment of the reaction conditions as was necessary for the syntheses of benzothiazoles.



Scheme 47: First attempt to the synthesis of imidazoline and benzimidazole.

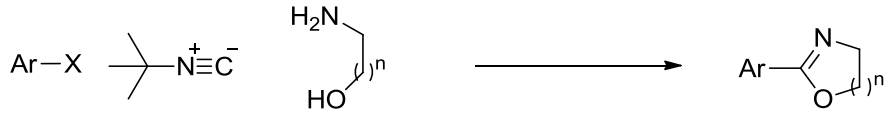
Various other nucleophiles could be tested under these reaction conditions. For example, employing nucleophilic substrates, such as hydroxyl-imidamides **2.56**, could lead to another types of heterocycles with a higher number of heteroatoms. This molecule has three nucleophilic centers which may react the same way as the ethanolamine does under the conditions developed, to lead to the formation of the corresponding oxadiazole **2.57** (Scheme 48).



Scheme 48: Potential synthesis of oxadiazole.

Finally, another interesting development could be studying the impact of the carbon chain length between the two nucleophilic centres, and therefore varying the ring size of the final product (Scheme 49). As the length of this carbon chain can have an

impact on the cyclisation step, it should be interesting to study what is the optimal length for the carbon chain in this reaction.



Scheme 49: Potential application to a larger ring size.

The method which has been developed was shown to be efficient in the synthesis of various heterocycles so far. But it also leaves a wide open field of investigation for the multicomponent synthesis of heterocycles. This work and its potential development can be of high interest for the rapid access to a number of scaffolds, which is crucial for the chemical library synthesis in the discovery of new lead compounds in both the pharmaceutical and agrochemical industry.

3 Experimental section.

The proton (^{1}H) and carbon (^{13}C) NMR spectra were recorded on a Bruker AV400 or a Bruker AV500 spectrometer . They were recorded either at 400.13 MHz or 500.13 MHz for the proton, and 100.61 MHz for the carbon. The chemical shifts are quoted in parts per million (ppm) and the coupling constants in Hertz (Hz). They are referenced to tetramethylsilane but calibrated on the solvent residual signal.

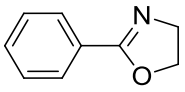
The normal resolution mass spectra of the compounds were recorded on a Thermofinnigan LCQ DUO LDU mass spectrometer using electrospray ionization (ESI) at the Strathclyde University Mass Spectrometry Service. The high resolution mass spectra were recorded at the EPSRC National Mass Spectrometry Service Centre, Swansea on a JLZX 102, VGZAB-E or a VG micromass instrument. The IR spectra were obtained from films applied on NaCl plates or from pressed disks using potassium bromide (KBr) as a matrix. A Perkin-Elmer Spectrum One FT-IR spectrometer was employed to record those spectra. Melting points were obtained using Gallencamp Griffin SG94/05/530 apparatus.

All reagents were obtained from commercial suppliers and used without any further purification, except for the 2-aminothiophenol, which was redistilled under reduced pressure from a bottle of the commercially available material. Dried toluene, tetrahydrofuran and diethyl ether were obtained from a Pure-Solv 400 solvent purification system from Innovative Technology Inc., USA. Dry dimethylformamide was obtained from commercial suppliers.

Purifications *via* column chromatography were performed using Silica gel 60 (200-400 mesh). "Concentrated *in vacuo*" refers to the evaporations of volatile species on a rotary evaporator instrumentation using a diaphragm pump vacuum.

3.1 Synthesis of 2-substituted Oxazolines

Preparation of 2-phenyl-4,5-dihydrooxazole **2.3a**



From iodobenzene :

1,1'-Bis(diphenylphosphino)ferrocene (27.8 mg , 0.05 mmol, 0.05 equiv.) and Cs_2CO_3 (423 mg, 1.3 mmol, 1.3 equiv.) were suspended in 5 ml of dry and degassed toluene in an oven-dried flask. Iodobenzene (0.11 mL, 1.0 mmol, 1.0 equiv.), *tert*-butylisocyanide (0.17 mL, 1.5 mmol, 1.5 equiv.) and ethanolamine (0.30 mL, 5 mmol, 5 equiv.) were syringed into the flask. $PdCl_2$ (8.9 mg, 0.05mmol, 5 mol%.) was added to the mixture, which was refluxed for 2h under argon. The mixture was then concentrated *in vacuo* and the residue was purified by column chromatography on silica, using a gradient from 0:1 to 3:7 of ethyl acetate/petroleum ether. This afforded the oxazoline **2.3a** (118 mg, 80%) as a colorless oil. (Lit.[72]) υ_{max}(film)/cm^{-1} 2935, 1649, 1355, 1257, 1082, 1064, 947, 698 ^{1}H-NMR (500 MHz, $CDCl_3$) 4.07 (2H, t, *J*= 9.5 Hz, CH_2) 4.45 (2H, t, *J* = 9.5 Hz, CH_2), 7.42 (2H, t, *J* = 8 Hz, ArH), 7.48 (1H, m, *J*=8 Hz, ArH), 7.96 (2H, d, *J* = 8 Hz, ArH); ^{13}C-NMR (100MHz, $CDCl_3$) δ 55.0 (CH_2) 67.6 (CH_2) 127.8 (C) 128.2 (CH) 131.3 (CH) 164.6 (C). *m/z* (ESI) 148 ($M + H^+$, 100 %).

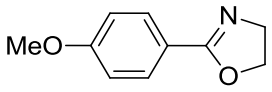
From Bromobenzene:

1,1'-Bis(diphenylphosphino)ferrocene (27.8 mg , 0.05 mmol, 0.05 equiv.) and Cs_2CO_3 (423 mg, 1.3 mmol, 1.3 equiv.) were suspended in 5 ml of dry and degased toluene in an oven dried flask. Bromobenzene (0.10 mL, 1.0 mmol, 1.0 equiv.), *tert*-butylisocyanide (0.17 mL, 1.5 mmol, 1.5 equiv.) and ethanolamine (0.30 mL, 5 mmol, 5 equiv.) were syringed into the flask. $PdCl_2$ (8.9 mg, 0.05mmol, 5 mol%) was added to the mixture, which was refluxed for 2 h under argon. The mixture was

then concentrated *in vacuo* and the residue was purified by column chromatography on silica, using a gradient of ethyl acetate:petroleum ether, 0:1 to 2:3. This afforded the oxazoline (113 mg, 77%) as a colorless oil. (Lit.[72]) υ_{max}(film)/cm^{-1} 2935, 1649, 1355, 1257, 1082, 1064, 947, 698 ^{1}H-NMR (500 MHz, $CDCl_3$) 4.07 (2H, t, *J*= 9.5 Hz, CH_2) 4.45 (2H, t, *J* = 9.5 Hz, CH_2), 7.42 (2H, t, *J* = 8 Hz, ArH), 7.48 (1H, m, *J*= 8 Hz, ArH), 7.96 (2H, d, *J* = 8 Hz, ArH); ^{13}C-NMR (100MHz, $CDCl_3$) δ 55.0 (CH_2) 67.6 (CH_2) 127.8 (CH) 128.2 (CH) 131.3 (CH) 164.6 (C). *m/z* (ESI) 148 (M + H$^+$, 100 %).

Preparation of 2-(4-methoxyphenyl)-4,5-dihydrooxazole **2.3d**

Reaction performed by Zoe Hamilton

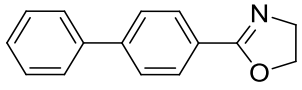


1,1'-Bis(diphenylphosphino)ferrocene (27.7 mg, 0.05 mmol, 0.05 equiv.) was added to an oven-dried flask containing a partial solution of cesium carbonate (422.5 mg, 1.3 mmol, 1.3 equiv.) in 5 mL toluene. The flask and condenser were then flushed with nitrogen for 10 min and 4-iodoanisole (234.0 mg, 1 mmol, 1 equiv.), *tert*-butyl isocyanide (0.17 mL, 1.5 mmol, 1.5equiv.) then ethanolamine (0.30 mL, 5 mmol, 5equiv.) were added. Palladium chloride (8.9 mg, 5 mol%) was then added and the reaction mixture was stirred under argon at 109 °C. After 2 h, the reaction mixture was left to cool to room temperature and then dried *in vacuo*. The resultant brown oil was purified using column chromatography (gradient elution from pure hexane to ethyl acetate:hexane 2 : 5. The product was obtained as a yellow-orange solid (122 mg, 0.69 mmol, 69 %). M.p. 55 – 57 °C (lit[73] m.p. = 56-58°C). ν_{max} (ATR)/cm^{-1} 2975, 2936, 290, 2876, 2839, 1649, 1614, 1509, 1357, 1252, 1166, 1069, 1019, 941, 833, 736, 672; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.85 (3H, s, CH_3), 4.04 (2H, t, *J* = 9.5 Hz, CH_2), 4.41 (2H, t, *J* = 9.5 Hz, CH_2), 6.92 (2H, d, *J* = 7.2 Hz, ArH), 7.90 (2H, d, *J* = 7.2, ArH); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 54.4 (CH_2), 54.8 (CH_2), 67.0 (CH_3), 113.2 (CH), 119.8 (C), 129.4(CH), 161.5 (C), 163.9 (C) ; *m/z* (ESI) 178 (M + H$^+$, 100 %)

From 4-methoxyphenyl trifluoromethanesulfonate:

1,1'-Bis(diphenylphosphino)ferrocene (27.8 mg , 0.05 mmol, 0.05 equiv.) and Cs_2CO_3 (423 mg, 1.3 mmol, 1.3 equiv.) were suspended in 5 ml of dry and degased toluene in an oven dried flask. 4-methoxyphenyl trifluoromethanesulfonate (0.18 mL, 1.0 mmol, 1.0 equiv.), *tert*-butylisocyanide (0.17 mL, 1.5 mmol, 1.5 equiv.) and ethanolamine (0.30mL, 5 mmol, 5 equiv.) were syringed into the flask. $PdCl_2$ (8.9 mg, 0.05 mmol, 5 mol%) was added to the mixture, which was refluxed for 2 h under argon. The mixture was then concentrated *in vacuo* and the residue was purified by column chromatography on silica using a gradient of ethyl acetate:petroleum ether, 1:9 to 1:1.. The oxazoline (126 mg, 71%) was obtained as a white solid. M.p. 55–57 °C (lit.[73] m.p. = 56-58°C). ν_{max} (ATR)/cm^{-1} 2975, 2936, 290, 2876, 2839, 1649, 1614, 1509, 1357, 1252, 1166, 1069, 1019, 941, 833, 736, 672; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.85 (3H, s, CH_3), 4.04 (2H, t, *J* = 9.5 Hz, CH_2), 4.41 (2H, t, *J* = 9.5 Hz, CH_2), 6.92 (2H, d, *J* = 7.2 Hz, ArH), 7.90 (2H, d, *J* = 7.2, ArH); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 54.4 (CH_2), 54.8 (CH_2), 67.0 (CH_3), 113.2 (CH), 119.8 (CH), 129.4(CH), 161.5 (C), 163.9 (C) ; *m/z* (ESI) 178 ($M + H^+$, 100 %)

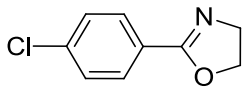
Preparation of 2-([1,1'-biphenyl]-4-yl)-4,5-dihydrooxazole **2.3f**.



1,1'-Bis(diphenylphosphino)ferrocene (27.8 mg , 0.05 mmol, 0.05 equiv.) and Cs_2CO_3 (423 mg, 1.3 mmol, 1.3 equiv.) were suspended in 5 ml of dry and degased toluene in an oven dried flask. 4-Bromo-1,1'-biphenyl (233 mg, 1.0 mmol, 1.0 equiv.), *tert*-butylisocyanide (0.17 mL, 1.5 mmol, 1.5 equiv.) and ethanolamine (0.30 mL, 5 mmol, 5 equiv.) were syringed into the flask. Palladium dichloride (8.9 mg, 0.05 mmol, 5 mol%) was added to the mixture, which was refluxed for 2 h

under argon. The mixture was then concentrated *in vacuo* and the residue was purified by column chromatography on silica, using a gradient of ethyl acetate:petroleum ether, 1:9 to 2:3. The *oxazoline* (180 mg, 81%) was obtained as a white solid. M.p. = 114-116 °C; [Found: $[M + H]^+$ 224.1071, $C_{15}H_{14}NO$ requires 224.1075] υ_{max}(KBr)/cm^{-1} 3060, 2901, 1640, 1350, 1253, 1072, 850, 732, 690 ; ^{1}H-NMR (400 MHz, $CDCl_3$) 4.11 (2H, t, *J* = 9.5 Hz, CH_2), 4.48 (2H, t, *J* = 9.5 Hz, CH_2), 7.40 (1H, d, *J* = 7 Hz, ArH), 7.48 (2H, dd, *J* = 7 and 8.4 Hz, ArH) 7.66-7.84 (4H, m, ArH), 8.04 (2H, d, *J* = 8.4 Hz, ArH); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 54.5 (CH_2), 67.1 (CH_2), 126.1 (C), 126.5 (CH), 126.7 (CH), 127.4 (CH), 128.1 (CH), 128.4 (CH), 139.8 (C), 143.6 (C), 164.0 (C). *m/z* (ESI) 224 ($M + H^+$, 100 %), 225 (16 %).

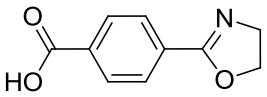
Preparation of 2-(4-chlorophenyl)-4,5-dihydrooxazole **2.3g**
Reaction performed by Zoe Hamilton



1,1'-Bis(diphenylphosphino)ferrocene (27.7 mg, 0.05 mmol, 0.05 equiv.) was added to an oven dried flask containing a partial solution of cesium carbonate (422.5 mg, 1.3 mmol, 1.3 equiv.) in 5 mL toluene. The flask and condenser were then flushed with nitrogen for 10 min and 1-chloro-4-iodobenzene (238.5 mg, 1 mmol, 1 equiv.), *tert*-butylisocyanide (0.17 mL, 1.5 mmol, 1.5 equiv.) and ethanolamine (0.30 mL, 5 mmol, 5 equiv.) were added. Palladium chloride (8.9 mg, 0.05 mmol, 5 mol%) was added and the reaction mixture was stirred under nitrogen at 109 °C. After 2 h, the reaction mixture was left to cool to room temperature. then dried *in vacuo*. The resultant brown oil was purified using column chromatography (gradient elution from pure hexane to ethyl acetate/hexane 2 : 5. The product obtained as off-white crystals (131.3 mg, 0.72 mmol, 72 %). M.p. 78 – 80°C (lit.[74] m.p. = 77-78°C) ν_{max} (ATR)/cm^{-1} 3087, 2986, 2932, 2908, 2878, 1649, 1599, 1485, 1403, 1360, 1260,

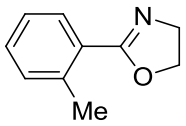
1213, 1012, 973, 941, 894, 840, 732, 665; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 4.06 ppm (2H, t, *J* = 9.4 Hz, CH_2), 4.43 (2H, t, *J* = 9.4 Hz, CH_2), 7.38 (2H, d, *J* = 8.4 Hz, ArH), 7.88 (2H, d, *J* = 8.4 Hz, ArH); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 54.3 (CH_2), 68.0 (CH_2), 126.5 (CH), 128.8 (C), 129.7 (CH), 137.7 (C), 164.0 (C); *m/z* (ESI) 182.00 ($M + H^+$, 100 %), 184.00 (34 %).

Preparation of 4-(4,5-dihydrooxazol-2-yl)benzoic acid **2.3h**



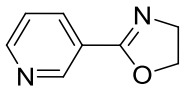
1,1'-Bis(diphenylphosphino)ferrocene (27.8 mg , 0.05 mmol, 0.05 equiv.) and Cs_2CO_3 (423 mg, 1.3 mmol, 1.3 equiv.) were suspended in 5 ml of dry and degassed toluene in an oven-dried flask. 4-Iodobenzoic acid (248 mg, 1.0 mmol, 1.0 equiv.), *tert*-butylisocyanide (0.17 mL, 1.5 mmol, 1.5 equiv.) and ethanolamine (0.30 mL, 5 mmol, 5 equiv.) were syringed into the flask. $PdCl_2$ (8.9 mg, 0.05 mmol, 5 mol%) was added to the mixture, which was refluxed for 2 h under argon. The mixture was then concentrated *in vacuo* and diluted with 30mL of ethyl acetate. This was washed with sodium bicarbonate solution (1M, 2 x 30 mL). The aqueous layer was acidified with acetic acid until pH = 5, and was then extracted with ethyl acetate (3 x 25 mL). The combined organics were washed with brine and dried on Na_2SO_4. It was then filtered and concentrated in vacuo to give a pale brown solid identified as the oxazoline (49 mg, 26%). M.p. = 181-182 °C (lit.[75] m.p. = 181°C) υ_{max}(KBr)/cm^{-1} 3417, 2906, 2490, 1700, 1640, 1608, 1281, 1091, 941, 708; ^{1}H-NMR (500 MHz, DMSO-d_6) δ 3.99 (2H, t, *J* = 9.5 Hz, CH_2) 4.43 (2H, t, *J* = 9.5 Hz, CH_2) 7.96 (2H, d, *J* = 8 Hz, ArH), 8.01 (2H, d, *J* = 8 Hz, ArH). ^{13}C-NMR (100 MHz, DMSO-d_6) δ 54.5 (CH_2) 67.6 (CH_2) 127.8 (CH) 129.5 (CH) 131.1 (C) 133.4 (C) 162.3 (C) 166.7 (C). *m/z* (ESI) 192 ($M + H^+$, 100 %)

Preparation of 2-(o-tolyl)-4,5-dihydrooxazole **2.3j**



1,1'-Bis(diphenylphosphino)ferrocene (27.8 mg , 0.05 mmol, 0.05 equiv.) and Cs_2CO_3 (423mg, 1.3 mmol, 1.3 equiv.) were suspended in dry and degassed toluene (5 ml) in an oven-dried flask. 2-Iodotoluene (0.13 mL, 1.0 mmol, 1.0 equiv.), *tert*-butylisocyanide (0.17 mL, 1.5 mmol, 1.5 equiv.) and ethanolamine (0.30 mL, 5 mmol, 5 equiv.) were added to the stirring mixture. $PdCl_2$ (8.9 mg, 0.05mmol, 5 mol%) was added to the mixture, which was refluxed overnight under an atmosphere of argon. The mixture was then concentrated *in vacuo* and the residue was purified by column chromatography on silica using a gradient of ethyl acetate:petroleum ether, 0:1 to 2:3.This afforded the oxazoline (114 mg, 69%) as a colorless oil. (Lit.[74]) υ_{max}(film)/cm^{-1} 2964, 1649, 1362, 1051, 944, 727; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 2.61 (3H, s, CH_3) 4.11 (2H, t, J = 9.5 Hz, CH_2), 4.38 (2H, t, J = 9.5 Hz, CH_2), 7.26 (2H, m, ArH) 7.33 (1H, t, J = 8 Hz, ArH), 7.81 (1H, d, J = 8 Hz, ArH) ^{13}C-NMR (100MHz, $CDCl_3$) δ 21.8 (CH_3), 55.4 (CH_2), 66.8 (CH_2), 125.5 (CH), 127.2 (C), 129.9 (CH), 130.4 (CH), 131.2 (CH), 138.7 (C), 165.1 (C), *m/z* (ESI) 162 ($M + H^+$, 100 %)

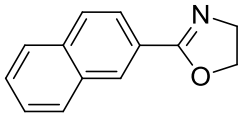
Preparation of 2-(pyridin-3-yl)-4,5-dihydrooxazole **2.3k**



1,1'-Bis(diphenylphosphino)ferrocene (27.8 mg , 0.05 mmol, 0.05 equiv.) and Cs_2CO_3 (423 mg, 1.3 mmol, 1.3 equiv.) were suspended in 5 ml of dry and degassed toluene in an oven-dried flask. 3-Bromopyridine (153 mg, 1.0 mmol, 1.0 equiv.), *tert*-butylisocyanide (0.17 mL, 1.5 mmol, 1.5 equiv.) and ethanolamine (0.30 mL, 5

mmol, 5 equiv.) were syringed into the flask. $PdCl_2$ (8.9 mg, 0.05 mmol, 0.05 equiv.) was added to the mixture, which was refluxed for 2 h under argon. The mixture was then concentrated *in vacuo* and the residue was purified by column chromatography on silica using a gradient of ethyl acetate:petroleum ether, 1:1 to 1:0. This afforded the oxazoline (136 mg, 93%) as brown solid. M.p. = 66-68°C (lit.[76] m.p.= 66-68°C) υ_{max}(KBr)/cm^{-1} 2934, 1651, 1418, 1360, 1262, 1078, 1023, 932, 702 ; ^{1}H-NMR (400 MHz, $CDCl_3$) 4.09 (2H, t, *J* = 9.5 Hz, CH_2), 4.47 (2H, t, *J* = 9.5 Hz, CH_2), 7.35 (1H, dd, *J* = 5 and 2 Hz, ArH), 8.21 (1H, ddd, *J* = 8 and 5 Hz, ArH), 8.70 (1H, dd, *J* = 8 and 2 Hz, ArH) 9.15 (1H, d, *J* = 2Hz); ^{13}C-NMR (100MHz, $CDCl_3$) δ 55.0 (CH_2), 67.8 (CH_2), 123.2 (CH), 123.9 (C), 135.5 (CH), 149.5 (CH), 152.0 (CH), 162.7 (C) ; *m/z* (ESI) 149 (M + H$^+$, 100 %)

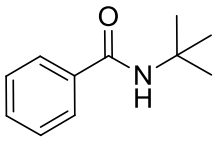
Preparation of 2-(naphthalen-2-yl)-4,5-dihydrooxazole **2.3l**.



1,1'-Bis(diphenylphosphino)ferrocene (27.8 mg , 0.05 mmol, 0.05 equiv.) and Cs_2CO_3 (423mg, 1.3 mmol, 1.3 equiv.) were suspended in 5 ml of dry and degassed toluene in an oven-dried flask. 2-Bromonaphthalene (207 mg, 1.0 mmol, 1.0 equiv.), *tert*-butylisocyanide (0.17 mL, 1.5 mmol, 1.5 equiv.) and ethanolamine (0.30mL, 5 mmol, 5 equiv.) were introduced into the flask. $PdCl_2$ (8.9mg, 0.05mmol, 5 mol%) was finally added to the mixture, which was refluxed for 2 h under argon. The mixture was then concentrated *in vacuo* and the residue was purified by column chromatography on silica, using a gradient of ethyl acetate:petroleum ether, 0:1 to 2:3. This afforded the oxazoline (172 mg, 88%) as white solid. M.p.= 84-85°C (lit.[77] m.p. = 85.5-86.5°C) υ_{max}(KBr)/cm^{-1}, 2972, 1643, 1360, 1059, 952, 828, 747; ^{1}H-NMR (400 MHz, $CDCl_3$) 4.14 (2H, t, *J* = 9.5 Hz, CH_2), 4.52 (2H, t, *J* = 9.5 Hz, CH_2), 7.55 (2H, m, ArH), 7.89 (2H, d, *J* = 7 Hz, ArH), 7.93 (1H, d, *J* = 7 Hz, ArH), 8.06 (1H, d, *J* = 7 Hz, ArH), 8.47 (1H, s, ArH); ^{13}C-NMR (100MHz, $CDCl_3$) δ 54.6 (CH_2), 67.2 (CH_2), 124.3 (CH), 124.6 (C), 126.0 (CH), 127.0 (CH), 127.3 (CH),

127.6 (CH), 128.1 (CH), 128.4 (CH), 132.2 (C), 134.2 (C), 164.26 (C); *m/z* (ESI) 199 ($M + H^+$, 100 %)

By-product isolated **2.19** from the reaction of iodobenzene and ethanolamine.

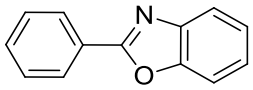


This product is the result of the hydrolysis of the iminoacyl palladium complex. It has therefore been isolated from a reaction where water has not been removed correctly. It is however evidence of the formation of the iminoacyl palladium complex.

1,1'-Bis(diphenylphosphino)ferrocene (27.8 mg , 0.05 mmol, 0.05 equiv.) and Cs_2CO_3 (423 mg, 1.3 mmol, 1.3 equiv.) were suspended in degassed toluene (5ml) in an oven-dried flask. Iodobenzene (0.11 mL, 1.0 mmol, 1.0 equiv.), *t*-butylisocyanide (0.17 mL, 1.5 mmol, 1.5 equiv.) and ethanolamine (0.30 mL, 5 mmol, 5 equiv.) were added to the stirring mixture. $PdCl_2$ (8.9 mg, 0.05 mmol, 5 mol%) was added to the mixture, which was refluxed overnight under an atmosphere of argon. The mixture was then concentrated *in vacuo* and the residue was purified by column chromatography on silica, using a gradient of ethyl acetate:petroleum ether, 0:1 to 2:3. This afforded *N*-(*tert*-butyl)benzamide (122 mg, 69%) as a solid. M.p =133-134 °C (lit[78] m.p = 133-135 °C); υ_{max}(KBr)/cm^{-1} 3318, 1927, 1635, 1536, 1489, 1311, 1218, 716, 694; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 1.49 (9H, s, CH_3), 5.97 (1H, broad s, NH), 7.43 (2H, t, J = 8 Hz, ArH), 7.48 (1H, t, J = 8 Hz, ArH), 7.74 (2H, d, J = 8 Hz, ArH), ^{13}C-NMR (100 MHz, $CDCl_3$) δ 28.4 (CH_3), 51.1 (C), 126.2 (CH), 128.0 (CH), 130.6 (CH), 135.4 (C), 166.4 (C), ESI MS: *m/z* 200 $[C_{11}H_{15}NO + Na]^+$.

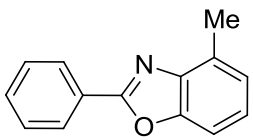
3.2 Synthesis of benzoxazoles.

Preparation of 2-phenylbenzoxazole **2.21**



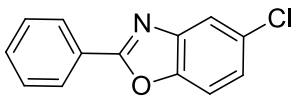
1,1'-Bis(diphenylphosphino)ferrocene (27.8 mg , 0.05 mmol, 0.05 equiv.) and Cs_2CO_3 (423 mg, 1.3 mmol, 1.3 equiv.) were suspended in 5 ml of dry and degassed toluene in an oven-dried flask. Iodobenzene (0.10 mL, 1.0 mmol, 1.0 equiv.), *tert*-butylisocyanide (0.17 mL, 1.5 mmol, 1.5 equiv.) and 2-aminophenol (545 mg, 5 mmol, 5 equiv.) were added to the stirring mixture. $PdCl_2$ (8.9 mg, 0.05 mmol, 5 mol%) was added to the mixture, which was refluxed for 2 h under an atmosphere of argon. The mixture was then concentrated *in vacuo* and the residue was purified by column chromatography on silica, using a gradient of ethyl acetate:petroleum ether, 0:1 to 1:9, to afford the benzoxazole (185 mg, 95%) as a white solid. M.p. = 101-102 °C (lit.[79] m.p. = 101-102 °C) υ_{max}(KBr)/cm^{-1} 3060, 1613, 1547, 1445, 1240, 1050, 921, 743, 683 ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.39 (2H, dd, J = 7.2 Hz, J = 3.2Hz Ar-H), 7.56 (3H, m, Ar-H), 7.61 (1H, dd, J = 7.2 and 3.2 Hz, Ar-H), 7.81 (1H, m, Ar-H), 8.29 (2H, m, Ar-H) ^{13}C-NMR (100MHz, $CDCl_3$) δ 110.0 (CH), 119.5 (CH), 124.0 (CH), 124.6 (CH), 126.7 (C), 127.1 (CH), 128.4 (CH), 131.0 (CH), 141.6 (C), 150.2 (C), 162.5 (C). *m/z* (ESI) 196 ($M + H^+$, 100 %), 197 (16%).

Preparation of 4-methyl-2-phenylbenzoxazole **2.25**.



1,1'-Bis(diphenylphosphino)ferrocene (27.8 mg , 0.05 mmol, 0.05 equiv.) and Cs_2CO_3 (423 mg, 1.3 mmol, 1.3 equiv.) were suspended in 5 ml of dry and degassed toluene in an oven dried flask. Iodobenzene (0.10 mL, 1.0 mmol, 1.0 equiv.), *t*-butylisocyanide (0.17 mL, 1.5 mmol, 1.5 equiv.) and 2-amino-*m*-cresol (615 mg, 5 mmol, 5 equiv.) were added to the stirred mixture. $PdCl_2$ (8.9mg, 0.05mmol, 5 mol%) was added to the mixture, which was refluxed for 2 h under an atmosphere of argon. The mixture was then concentrated *in vacuo* and the residue was purified by column chromatography on silica, using a gradient of ethyl acetate:petroleum ether, 0:1 to 1:9. This afforded the benzoxazole **2.25** (198 mg, 96%) as a pinkish solid. M.p. = 90-92 °C (lit.[80] m.p. = 92-93 °C); υ_{max}(KBr)/cm^{-1} 3049, 1621, 1550, 1484, 1445, 1059, 776, 757, 699, 683 ; ^{1}H-NMR 400 MHz, $CDCl_3$) δ 2.70 (3H, s, CH_3), 7.17 (1H, d ,*J* = 7.6 Hz, Ar-H), 7.26 (1H, t, *J* = 7.6 Hz, ArH) 7.43 (1H, d, *J* = 7.6 Hz, ArH), 7.55 (3H, m, ArH), 8.29 (2H, m, ArH); ^{13}C-NMR (100MHz, $CDCl_3$) δ 16.1 (CH_3), 107.4 (CH), 124.2 (CH), 124.6 (CH), 127.0 (C), 127.1 (CH), 128.3 (CH), 130.1 (C), 130.8 (CH), 140.1 (C), 150.0 (C), 161.8 (C). *m/z* (ESI) 210 ($M + H^+$, 100 %)

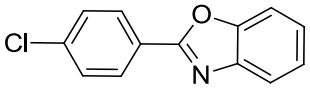
Preparation of 5-chloro-2-phenylbenzoxazole **2.27**.



1,1'-Bis(diphenylphosphino)ferrocene (27.8 mg , 0.05 mmol, 0.05 equiv.) and Cs_2CO_3 (423 mg, 1.3 mmol, 1.3 equiv.) were suspended in 5 ml of dry and degased toluene in an oven dried flask. Iodobenzene (0.10 mL, 1.0 mmol, 1.0 equiv.), *t*-butylisocyanide (0.17 mL, 1.5 mmol, 1.5 equiv.) and 4-chloro-2-aminophenol (715 mg, 5 mmol, 5 equiv.) were added to the stirring mixture. $PdCl_2$ (8.9mg, 5 mol%) was added to the mixture, which was refluxed for 2 h under an atmosphere of argon. The mixture was then concentrated *in vacuo* and the residue was purified by column chromatography on silica, using a gradient of ethyl acetate:petroleum ether, 0:1 to 1:9. This afforded the benzoxazole **2.27** (224 mg, 98%) as a white solid. M.p. = 104-

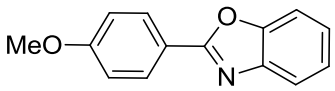
106 °C (lit.[79] m.p. =107-108 °C) υ_{max}(KBr)/cm^{-1} 3054, 1882, 1610, 1552, 1445, 1050, 809, 699 ; ^{1}H-NMR 400 MHz, $CDCl_3$) δ 7.34 (1H, dd, *J* = 8Hz and 2Hz, ArH), 7.55 (4H, m, ArH), 7.77 (1H, d, *J* = 2 Hz, ArH), 8.25 (2H, dd, *J* = 8 Hz, *J* = 2Hz, ArH) ^{13}C-NMR (100 MHz, $CDCl_3$) 110.8 (CH), 119.5 (CH), 124.9 (CH), 126.2 (C), 127.2 (CH), 128.5 (CH), 129.5 (C), 131.4 (CH), 142.8 (C), 148.8 (C), 163.9 (C). *m/z* (ESI) 230 (M + H$^+$, 100 %), 232 (33%)

Preparation of 2-(4-chlorophenyl)benzoxazole **2.33**.



1,1'-Bis(diphenylphosphino)ferrocene (27.8 mg , 0.05 mmol, 0.05 equiv.) and Cs_2CO_3 (423 mg, 1.3 mmol, 1.3 equiv.) were suspended in 5 ml of dry and degased toluene in an oven dried flask. 4-Chloro-iodobenzene (238 mg, 1.0 mmol, 1.0 equiv.), *t*-butylisocyanide (0.17 mL, 1.5 mmol, 1.5 equiv.) and 2-aminophenol (545 mg, 5 mmol, 5 equiv.) were added to the stirring mixture. $PdCl_2$ (8.9 mg, 0.05 mmol, 5 mol%) was added to the mixture, which was refluxed for 2 h under an atmosphere of argon. The mixture was then concentrated *in vacuo* and the residue was purified by column chromatography on silica using a gradient of ethyl acetate:petroleum ether, 0:1 to 1:9. This afforded the benzoxazole (211 mg, 92%) as a white solid. M.p. = 158-150 °C (lit.[79] m.p. = 148-150 °C) υ_{max}(KBr)/cm^{-1} 3054, 1613, 1596, 1481, 1451, 1089, 1056, 381, 738 ; ^{1}H-NMR 400 MHz, $CDCl_3$) δ 7.39 (2H, dd, *J* = 3.2 Hz, ArH), 7.53 (2H, d, *J* = 8.4 Hz, ArH), 7.61 (1H, t, *J* = 3.2 Hz, ArH), 7.94 (1H, m, ArH), 8.22 (2H, d, *J* = 8.4 Hz, ArH); ^{13}C-NMR (100MHz, $CDCl_3$) 110.1 (CH), 119.6 (CH), 124.2 (CH), 127.9 (CH), 125.2 (C), 128.4 (CH), 128.8 (CH), 137.3 (C), 141.5 (C), 150.3 (C), 161.5 (C). *m/z* (ESI) 230 (M + H$^+$, 100 %), 232 (33%)

Preparation of 2-(4-methoxyphenyl)benzoxazole **2.35**

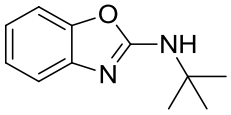


1,1'-Bis(diphenylphosphino)ferrocene (27.8 mg , 0.05 mmol, 0.05 equiv.) and Cs_2CO_3 (423 mg, 1.3 mmol, 1.3 equiv.) were suspended in 5 ml of dry and degased toluene in an oven dried flask. 4-bromoanisole (0.10 mL, 1.0 mmol, 1.0 equiv.), *t*-butylisocyanide (0.17 mL, 1.5 mmol, 1.5 equiv.) and 2-aminophenol (545 mg, 5 mmol, 5 equiv.) were added to the stirring mixture. $PdCl_2$ (8.9 mg, 0.05 mmol, 5 mol%) was added to the mixture, which was refluxed for 2 h under an atmosphere of argon. The mixture was then concentrated *in vacuo* and the residue was purified by column chromatography on silica, using a gradient of ethyl acetate:petroleum ether, 0:1 to 1:9. This afforded the benzoxazole (225 mg, 99%) as a white solid. M.p. = 96-98 °C (lit.[79] m.p. = 98 °C); υ_{max}(KBr)/cm^{-1} 1615, 1602, 1503, 1454, 1256, 1242, 1168, 1017, 831, 740, 729; ^{1}H-NMR 400 MHz, $CDCl_3$) δ 3.92 (3H, s, OCH_3), 7.05 (2H, d, *J* = 8.8 Hz, ArH), 7.35 (2H, m, ArH), 7.58 (1H, m, ArH), 7.76 (1H, m, ArH), 8.22 (2H, d, *J* = 8.8 Hz, ArH); ^{13}C-NMR (100MHz, $CDCl_3$) 55.0 (CH_3), 110.0 (CH), 113.9 (CH), 119.1 (CH), 119.3 (C), 123.9 (CH), 124.1 (CH), 128.9 (CH), 141.8 (C), 150.2 (C), 161.8 (C), 162.7 (C). *m/z* (ESI) 226 ($M + H^+$, 100 %).

3.3 Synthesis of Benzothiazoles.

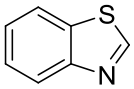
Control reactions:

N-(*tert*-butyl)benzoxazol-2-amine **2.43**:



1,1'-Bis(diphenylphosphino)ferrocene (27.8 mg , 0,05 mmol, 0.05 equiv.) and Cs_2CO_3 (423 mg, 1.3 mmol, 1.3 equiv.) were suspended in 5 ml of dry and degassed toluene in an oven-dried flask. *tert*-Butylisocyanide (0.17 mL, 1.5 mmol, 1.5 equiv.) and 2-aminophenol (545 mg, 5 mmol, 5 equiv.) were added to the stirring mixture. $PdCl_2$ (8.9mg, 0.05mmol, 5 mol%) was added to the mixture, which was refluxed for 2 h under an atmosphere of argon. The mixture was then concentrated *in vacuo* and the residue was purified by column chromatography on silica, using ethyl acetate: petroleum ether 1:9 to afford the benzoxazole (43 mg, 23%) as a white solid. m.p. = 100-102 °C (lit.[81] m.p. = 101-102 °C); ^{1}H-NMR (400 MHz, $CDCl_3$) δ 1.52 (9H, s, CH_3) 5.12 (1H, broad s, NH), 7.04 (1H, t, *J* = 8 Hz, ArH), 7.17 (1H, t, *J* = 8 Hz, ArH), 7.26 (1H, d, *J* = 8 Hz, ArH), 7.40 (1H, d, *J* = 8 Hz, ArH), ^{13}C-NMR (100 MHz, $CDCl_3$) δ 28.7 (CH_3), 51.5 (C), 108.0 (CH), 115.6 (CH), 120.1 (CH) 123.1 (CH), 142.7 (C), 147.6 (C), 160.3 (C), ESI MS: *m/z* 191 $[M + H]^+$.

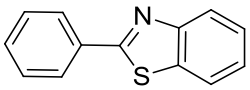
Benzothiazole **2.39**:



1,1'-Bis(diphenylphosphino)ferrocene (27.8mg , 0,05 mmol, 0.05 equiv.) and Cs_2CO_3 (423mg, 1.3 mmol, 1.3 equiv.) were suspended in 5 ml of dry and degased toluene in an oven dried flask. *tert*-butylisocyanide (0.17 mL, 1.5 mmol, 1.5 equiv.) and 2-aminothiophenol (545 mg, 5 mmol, 5 equiv.) were added to the stirring

mixture. $PdCl_2$ (8.9mg, 0.05mmol, 5 mol%) was added to the mixture, which was refluxed for 2h under an atmosphere of argon. The mixture was then concentrated *in vacuo* and the residue was purified by column chromatography on silica, using ethyl acetate in petroleum ether 1:9 to afford the benzothiazole (84 mg, 62%). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.43 (1H, t, J = 10 Hz, ArH), 7.51 (1H, t, J = 10 Hz, ArH), 7.94 (1H, d, J = 10 Hz, ArH), 8.16 (1H, d, J = 10 Hz, ArH), 9.00 (1H, *s*, ArH), ^{13}C-NMR (100 MHz, $CDCl_3$) δ 121.9 (CH), 123.6 (CH), 125.5 (CH), 126.1 (CH), 133.7 (C) 153.2 (C), 153.9 (CH), *m/z* (ESI) 136 (M + H^+, 100 %) (lit.[82])

Preparation of 2-phenylbenzothiazole **2.38**.



Method A: 1,1'-Bis(diphenylphosphino)ferrocene (27.8mg , 0,05 mmol, 0.05 equiv.) and Cs_2CO_3 (423mg, 1.3 mmol, 1.3 equiv.) were suspended in 5 ml of dry and degassed DMF in an oven dried flask. Iodobenzene (0.11 mL, 1.0 mmol, 1.0 equiv.), *tert*-butylisocyanide (0.17 mL, 1.5 mmol, 1.5 equiv.) and 2-aminothiophenol (0.28 mL, 5 mmol, 5 equiv.) were added to the stirring mixture. $PdCl_2$ (8.9 mg, 0.05 mmol, 5 mol%) and CuBr (28.7 mg, 0.2 mmol, 0.2 equiv.) was added to the mixture, which was refluxed for 4 h under an atmosphere of argon. The mixture was then concentrated in vacuo and the residue was purified by column chromatography on silica, using a gradient from pure petroleum ether to ethyl acetate:petroleum ether 1:9. The resulting solid was re-crystallized in *n*-hexane. This afforded the benzothiazole (59 mg, 28%) as crystalline colorless needles. *(for data see p73)*

Method B: 1,1'-Bis(diphenylphosphino)ferrocene (27.8 mg , 0,05 mmol, 0.05 equiv.) and Cs_2CO_3 (423mg, 1.3 mmol, 1.3 equiv.) were suspended in 5 ml of dry and degassed DMF in an oven-dried flask. Iodobenzene (0.10 mL, 1.0 mmol, 1.0 equiv.), *tert*-butylisocyanide (0.17 mL, 2.5 mmol, 2.5 equiv.) and 2-

aminothiophenol (0.28 mL, 2.5 mmol, 2.5 equiv.) were added to the stirring mixture. $PdCl_2$ (8.9 mg, 0.05 mmol, 5 mol%) and CuBr (28.7 mg, 0.2 mmol, 0.2 equiv.) was added to the mixture, which was refluxed for 4 h under an atmosphere of argon. Once cooled down, the reaction mixture was diluted in DCM(20 mL) and washed with a solution of NaOH (1M, 2x25 mL), water (25 mL) and brine (25 mL). The organic layer was dried over Na_2SO_4. It was then filtered and concentrated *in vacuo* and the residue was purified by column chromatography on silica, using a gradient from pure petroleum ether to ethyl acetate:petroleum ether 1:9. The resulting solid was re-crystallized in *n*-hexane. This afforded the benzothiazole (69 mg, 33%) as crystalline colorless needles. *(for data see p73)*

Method C: Tri-*tert*-butylphosphine (20.23 mg , 0.1 mmol, 0.1 equiv.) and Cs_2CO_3 (423mg, 1.3 mmol, 1.3 equiv.) were suspended in 5ml of dry and degassed DMF in an oven-dried flask. Iodobenzene (0.11 mL, 1.0 mmol, 1.0 equiv.), *tert*-butylisocyanide (0.17 mL, 1.5 mmol, 1.5 equiv.) and 2-aminothiophenol (0.28 mL, 5 mmol, 5 equiv.) were added to the stirring mixture. $PdCl_2$ (8.9 mg, 0.05 mmol, 5 mol%) and CuBr (28.7 mg, 0.2 mmol, 0.2 equiv.) was added to the mixture, which was refluxed for 4 h under an atmosphere of argon. Once cooled down, the reaction mixture was diluted in DCM (20mL) and washed with a solution of NaOH (1M, 2x25 mL), water (25 mL) and brine (25 mL). The organic layer was dried over Na_2SO_4. It was then filtered and concentrated *in vacuo* and the residue was purified by column chromatography on silica, using a gradient from pure petroleum ether to ethyl acetate:petroleum ether 1:9. The resulting solid was re-crystallized in *n*-hexane. This afforded the benzothiazole (10 mg, 5%) as crystalline colorless needles. *(for data see p73)*

Method D: 1,1'-Bis(diphenylphosphino)ferrocene (27.8 mg , 0,05 mmol, 0.05 equiv.) and Cs_2CO_3 (423 mg, 1.3 mmol, 1.3 equiv.) were suspended in 5 ml of dry and degassed DMF in an oven-dried flask. Iodobenzene (0.11 mL, 1.0 mmol, 1.0 equiv.), *tert*-butylisocyanide (0.17 mL, 1.5 mmol, 1.5 equiv.) and 2-aminothiophenol (0.28 mL, 5 mmol, 5 equiv.) were added to the stirring mixture. $Pd(OAc)_2$ (8.9 mg, 0.05 mmol, 5 mol%) and CuBr (28.7 mg, 0.2 mmol, 0.2 equiv.)

was added to the mixture, which was refluxed for 4 h under an atmosphere of argon. Once cooled down, the reaction mixture was diluted in DCM (20 mL) and washed with a solution of NaOH (1M, 2x25 mL), water (25 mL) and brine (25 mL). The organic layer was dried over Na_2SO_4. It was then filtered and concentrated *in vacuo* and the residue was purified by column chromatography on silica, using a gradient from pure petroleum ether to ethyl acetate:petroleum ether 1:9. The resulting solid was re-crystallized in *n*-hexane. This afforded the benzothiazole (76 mg, 36%) as crystalline colorless needles. *(for data see p73)*

Method E: 1,1'-Bis(diphenylphosphino)ferrocene (27.8 mg , 0,05 mmol, 0.05 equiv.) and Cs_2CO_3 (423 mg, 1.3 mmol, 1.3 equiv.) were suspended in 5 ml of dry and degassed DMF in an oven-dried flask. Iodobenzene (0.11 mL, 1.0 mmol, 1.0 eq.), *t*-butylisocyanide (0.17 mL, 2.5 mmol, 2.5 equiv.) and 2-aminothiophenol (0.28 mL, 2.5 mmol, 2.5 equiv.) were added to the stirring mixture. $Pd(OAc)_2$ (11.2 mg, 0.05 mmol, 5 mol%) and CuI (38.1 mg, 0.2 mmol, 0.2 equiv.) was added to the mixture, which was refluxed for 4 h under an atmosphere of argon. Once cooled down, the reaction mixture was diluted in ethyl acetate (20 mL) and washed with a solution of NaOH (1M, 2x25 mL), water (25 mL) and brine (25 mL). The organic layer was dried over Na_2SO_4. It was then filtered and concentrated *in vacuo* and the residue was purified by column chromatography on silica, using a gradient from pure petroleum ether to ethyl acetate:petroleum ether 1:9. The resulting solid was re-crystallized in *n*-hexane. This afforded the benzothiazole (84 mg, 40%) as crystalline colorless needles. *(for data see p73)*

Method F: 1,1'-Bis(diphenylphosphino)ferrocene (27.8mg , 0,05 mmol, 0.05 equiv.) and Cs_2CO_3 (423mg, 1.3 mmol, 1.3 equiv.) were suspended in 5 ml of dry and degassed DMF in an oven-dried flask. Bromobenzene (0.10 mL, 1.0 mmol, 1.0 equiv.), *tert*-butylisocyanide (0.17 mL, 2.5 mmol, 2.5 equiv.) and 2-aminothiophenol (0.28 mL, 2.5 mmol, 2.5 equiv.) were added to the stirring mixture. $Pd(OAc)_2$ (11.2 mg, 0.05 mmol, 5 mol%) and CuI (38.1 mg, 0.2 mmol, 0.2 equiv.) was added to the mixture, which was refluxed for 4 h under an atmosphere of argon. Once cooled down, the reaction mixture was diluted in ethyl acetate (20 mL) and

washed with a solution of NaOH (1M, 2x25 mL), water (25 mL) and brine (25 mL). The organic layer was dried over Na_2SO_4. It was then filtered and concentrated *in vacuo* and the residue was purified by column chromatography on silica, using a gradient from pure petroleum ether to ethyl acetate:petroleum ether 1:9. The resulting solid was re-crystallized in *n*-hexane. This afforded the benzothiazole (80 mg, 38%) as crystalline colorless needles. *(for data see p73)*

Method G: 1,1'-Bis(diphenylphosphino)ferrocene (27.8mg , 0,05 mmol, 0.05 equiv.) and 2,6-lutiidine (139 mg, 1.28 mL, 1.3 mmol, 1.3 equiv.) were suspended in 5 ml of dry and degassed DMF in an oven-dried flask. Iodobenzene (0.11 mL, 1.0 mmol, 1.0 equiv.), *tert*-butylisocyanide (0.17 mL, 2.5 mmol, 2.5 equiv.) and 2-aminothiophenol (0.28 mL, 2.5 mmol, 2.5 equiv.) were added to the stirring mixture. $Pd(OAc)_2$ (11.2 mg, 0.05 mmol, 5 mol%) and CuI (38.1mg, 0.2 mmol, 0.2 equiv.) was added to the mixture, which was refluxed for 4 h under an atmosphere of argon. Once cooled down, the reaction mixture was diluted in ethyl acetate (20mL) and washed with a solution of NaOH (1M, 2x25 mL), water (25 mL) and brine (25 mL). The organic layer was dried over Na_2SO_4. It was then filtered and concentrated *in vacuo* and the residue was purified by column chromatography on silica, using a gradient from pure petroleum ether to ethyl acetate:petroleum ether 1:9.. The resulting solid was recrystallized in *n*-hexane. This afforded the benzothiazole (84 mg, 40%) as crystalline colorless needles. *(for data see p73)*

Method H: 1,1'-Bis(diphenylphosphino)ferrocene (27.8 mg , 0,05 mmol, 0.05 equiv.) and triethylamine (130 mg, 0.98 mL, 1.3 mmol, 1.3 equiv.) were suspended in 5 ml of dry and degassed DMF in an oven-dried flask. Iodobenzene (0.11 mL, 1.0 mmol, 1.0 equiv.), *tert*-butylisocyanide (0.17 mL, 2.5 mmol, 2.5 equiv.) and 2-aminothiophenol (0.28mL, 2.5 mmol, 2.5 equiv.) were added to the stirring mixture. $Pd(OAc)_2$ (11.2 mg, 0.05 mmol, 5 mol%) and CuI (38.1 mg, 0.2 mmol, 0.2 equiv.) was added to the mixture, which was refluxed for 4 h under an atmosphere of argon. Once cooled down, the reaction mixture was diluted in ethyl acetate (20 mL) and washed with a solution of NaOH (1M, 2x25 mL), water (25 mL) and brine (25 mL). The organic layer was dried over Na_2SO_4. It was then filtered and concentrated *in*

vacuo and the residue was purified by column chromatography on silica, using a gradient from pure petroleum ether to ethyl acetate:petroleum ether 1:9. The resulting solid was re-crystallized in *n*-hexane. This afforded the benzothiazole (78 mg, 37%) as crystalline colorless needles. *(for data see p73)*

Method I: 1,1'-Bis(diphenylphosphino)ferrocene (27.8 mg , 0,05 mmol, 0.05 equiv.) and K_3PO_4 (210 mg, 1.3 mmol, 1.3 equiv.) were suspended in 5 ml of dry and degassed DMF in an oven-dried flask. Iodobenzene (0.11 mL, 1.0 mmol, 1.0 equiv.), *tert*-butylisocyanide (0.17 mL, 2.5 mmol, 2.5 equiv.) and 2-aminothiophenol (0.28 mL, 2.5 mmol, 2.5 equiv.) were added to the stirring mixture. $Pd(OAc)_2$ (11.2 mg, 0.05 mmol, 5 mol%) and CuI (38.1 mg, 0.2 mmol, 0.2 equiv.) was added to the mixture, which was refluxed for 4 h under an atmosphere of argon. Once cooled down, the reaction mixture was diluted in ethyl acetate (20 mL) and washed with a solution of NaOH (1M, 2x25 mL), water (25 mL) and brine (25 mL). The organic layer was dried over Na_2SO_4. It was then filtered and concentrated *in vacuo* and the residue was purified by column chromatography on silica, using a gradient from pure petroleum ether to ethyl acetate:petroleum ether 1:9. The resulting solid was re-crystallized in *n*-hexane. This afforded the benzothiazole (82mg, 39%) as crystalline colorless needles. *(for data see p73)*

Method J: 1,1'-Bis(diphenylphosphino)ferrocene (27.8 mg , 0,05 mmol, 0.05 equiv.) and Cs_2CO_3 (423mg, 1.3 mmol, 1.3 equiv.) were suspended in 5 ml of dry and degassed DMAc in an oven-dried flask. Iodobenzene (0.11 mL, 1.0 mmol, 1.0 eq.), *t*-butylisocyanide (0.17 mL, 2.5 mmol, 2.5 equiv.) and 2-aminothiophenol (0.28 mL, 2.5 mmol, 2.5 equiv.) were added to the stirring mixture. $Pd(OAc)_2$ (11.2 mg, 0.05 mmol, 5 mol%) and CuI (38.1 mg, 0.2 mmol, 0.2 equiv.) was added to the mixture, which was refluxed for 4 h under an atmosphere of argon. Once cooled down, the reaction mixture was diluted in ethyl acetate (20 mL) and washed with a solution of NaOH (1M, 2x25 mL), water (25 mL) and brine (25 mL). The organic layer was dried over Na_2SO_4. It was then filtered and concentrated *in vacuo* and the residue was purified by column chromatography on silica, using a gradient from pure petroleum ether to ethyl acetate:petroleum ether 1:9. The resulting solid was re-

crystallized in *n*-hexane. This afforded the benzothiazole (53 mg, 25%) as crystalline colorless needles. *(for data see below)*

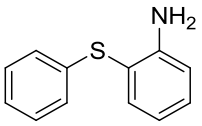
Method K: 1,1'-Bis(diphenylphosphino)ferrocene (27.8 mg , 0,05 mmol, 0.05 equiv.) and Cs_2CO_3 (423 mg, 1.3 mmol, 1.3 eq.) were suspended in 5 ml of dry and degassed DMF in an oven-dried flask. Iodobenzene (0.10 mL, 1.0 mmol, 1.0 equiv.), *tert*-butylisocyanide (0.17 mL, 1.5 mmol, 1.5 equiv.) and 2-aminothiophenol (0.28 mL, 2.5 mmol, 2.5 equiv.) were added to the stirring mixture. $Pd(OAc)_2$ (8.9 mg, 0.05 mmol, 5 mol%) and CuI (9.5 mg, 0.05 mmol, 0.05 equiv.) was added to the mixture, which was refluxed for 4 h under an atmosphere of argon. Once cooled down, the reaction mixture was diluted in Ethyl acetate (20 mL) and washed with a solution of NaOH (1M, 2x25 mL), water (25 mL) and brine (25 mL). The organic layer was dried over Na_2SO_4. It was then filtered and concentrated *in vacuo* and the residue was purified by column chromatography on silica, using a gradient from pure petroleum ether to ethyl acetate:petroleum ether 1:9. The fraction was concentrated to dryness and the resulting solid was re-crystallized in *n*-hexane. This afforded the benzothiazole (125mg, 59%) as crystalline colorless needles.

Physical and spectral data for 2-phenylbenzothiazole:

M.p. =110-112°C (lit.[79] m.p. = 110-112°C) υ_{max}(KBr)/cm^{-1} 3060, 1476, 1429, 1308, 1220, 957, 762, 683; ^{1}H-NMR 400 MHz, $CDCl_3$) δ 7.41 (1H, t, *J* = 8 Hz, ArH), 7.52 (4H, m, ArH) 7.94 (1H, d, *J* =8 Hz, ArH) 8.12 (3H, m, ArH) ^{13}C-NMR (100 MHz, $CDCl_3$) 121.1 (CH), 122.8 (CH), 124.6 (CH), 125.8 (CH), 127.1 (CH), 128.5 (CH), 130.5 (CH), 133.1 (C), 134.6 (C), 153.7 (C), 167.6 (C). *m/z* (ESI) 212 ($M + H^+$, 100 %)

By-product isolated from the Ullman coupling of iodobenzene and 2-aminothiophenol:

2-(phenylthio)aniline **2.47**:



This product is formed during the synthesis of benzothiazole. Its formation is due to the Ullman type reaction between the aryl-iodide and the 2-aminothiophenol which is catalysed by the Copper (I) Iodide in the reaction mixture. This was isolated during the purification of 2-phenylbenzothiazole by column chromatography. The amount of this aniline product observed was different depending on the method employed:

Method A: Not isolated but the formation of the compound observed by TLC.

Method B: Not isolated but the formation of the compound observed by TLC.

Method C: Not isolated but the formation of the compound observed by TLC.

Method D: 108 mg, 54% isolated as a yellow oil.

Method E: Not isolated but the formation of the compound observed by TLC.

Method F: 65 mg, 31 % isolated as a yellow oil.

Method G: Not isolated but the formation of the compound observed by TLC.

Method H: Not isolated but the formation of the compound observed by TLC.

Method I: 59 mg, 28% isolated as a yellow oil.

Method J: 77 mg, 36 % isolated as a yellow oil.

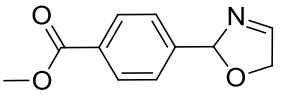
Method K: 45 mg, 21% isolated as a yellow oil.

Spectral data:

υ_{max}(film)/cm^{-1} 3461, 3351, 3049, 1604, 1470, 1443, 1306, 1157, 1072, 1023 ; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 4.34 (2H, broad s, NH_2), 6.83 (2H, *m*, ArH), 7.18 (3H, *m*, ArH), 7.30 (3H, *m*, ArH), 7.54 (1H, *d*, J= 8 Hz, ArH) ^{13}C-NMR (100 MHz, $CDCl_3$) δ 113.8 (C), 114.9 (CH), 118.3 (CH), 125.0 (CH), 126.0 (CH), 128.6 (CH), 130.7 (CH),136.40 (C), 137.06 (CH), 148.4 (C); *m/z* (ESI) 202 ($M + H^+$, 100 %

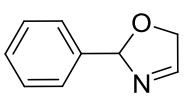
3.4 Unsuccessful reactions

Attempted preparation of methyl 4-(2,5-dihydrooxazol-2-yl)benzoate **2.3i**



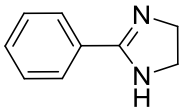
1,1'-Bis(diphenylphosphino)ferrocene (27.8 mg , 0.05 mmol, 0.05 equiv.) and Cs_2CO_3 (423 mg, 1.3 mmol, 1.3 equiv.) were suspended in 5 ml of dry and degassed toluene in an oven-dried flask. Methyl-4-iodobenzoate (262 mg, 1.0 mmol, 1.0 equiv.), *tert*-butylisocyanide (0.17 mL, 1.5 mmol, 1.5 equiv.) and ethane-1,2-diamine (0.32 mL, 5 mmol, 5 equiv.) were syringed into the flask. $PdCl_2$ (8.9 mg, 0.05mmol, 5 mol%) was added to the mixture, which was refluxed for 2h under argon. The mixture was then concentrated *in vacuo* and the residue was purified by column chromatography on silica, using a gradient from 0% to 100% of ethyl acetate in petroleum ether. No evidence of the presence of the expected product was found.

Attempted preparation of 2-phenylbenzoxazole **2.3a** from chlorobenzene **2.8**.



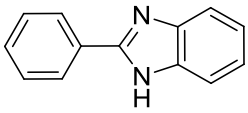
1,1'-Bis(diphenylphosphino)ferrocene (27.8 mg , 0.05 mmol, 0.05 equiv.) and Cs_2CO_3 (423 mg, 1.3 mmol, 1.3 equiv.) were suspended in 5 ml of dry and degassed toluene in an oven-dried flask. Chlorobenzene (1.3 mL, 1.0 mmol, 1.0 equiv.), *tert*-butylisocyanide (0.17 mL, 1.5 mmol, 1.5 equiv.) and ethane-1,2-diamine (0.32 mL, 5 mmol, 5 equiv.) were syringed into the flask. $PdCl_2$ (8.9 mg, 0.05mmol, 5 mol%) was added to the mixture, which was refluxed for 2h under argon. The mixture was then concentrated *in vacuo* and the residue was purified by column chromatography on silica, using a gradient from 0% to 100% of ethyl acetate in petroleum ether. No evidence of the presence of the expected product was found.

Attempted preparation of 2-phenyl-4,5-dihydro-1H-imidazole **2.53**.



1,1'-Bis(diphenylphosphino)ferrocene (27.8 mg , 0.05 mmol, 0.05 equiv.) and Cs_2CO_3 (423 mg, 1.3 mmol, 1.3 equiv.) were suspended in 5 ml of dry and degassed toluene in an oven-dried flask. Iodobenzene (0.11 mL, 1.0 mmol, 1.0 equiv.), *tert*-butylisocyanide (0.17 mL, 1.5 mmol, 1.5 equiv.) and ethane-1,2-diamine (0.32 mL, 5 mmol, 5 equiv.) were syringed into the flask. $PdCl_2$ (8.9 mg, 0.05mmol, 5 mol%) was added to the mixture, which was refluxed for 2h under argon. The mixture was then concentrated *in vacuo* and the residue was purified by column chromatography on silica, using a gradient from 0% to 100% of ethyl acetate in petroleum ether. The column was the flushed with 10 MeOH in DCM. No evidence of the presence of the expected product was found.

Preparation of 2-phenyl-1H-benzimidazole **2.55**.



1,1'-Bis(diphenylphosphino)ferrocene (27.8 mg , 0.05 mmol, 0.05 equiv.) and Cs_2CO_3 (423 mg, 1.3 mmol, 1.3 equiv.) were suspended in 5 ml of dry and degassed toluene in an oven-dried flask. Iodobenzene (0.10 mL, 1.0 mmol, 1.0 equiv.), *tert*-butylisocyanide (0.17 mL, 1.5 mmol, 1.5 equiv.) and *o*-phenylenediamine (540 mg, 5 mmol, 5 equiv.) were added to the stirring mixture. $PdCl_2$ (8.9 mg, 0.05 mmol, 5 mol%) was added to the mixture, which was refluxed for 2h under an atmosphere of argon. The mixture was then concentrated *in vacuo* and the residue was purified by column chromatography on silica, using a gradient from 0% to 100% of ethyl acetate in petroleum ether. The column was the flushed with 10 MeOH in DCM. No evidence of the presence of the expected product was found.

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