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Formation de liaisons C-C et C-hétéroatome par catalyse au cuivre ou en présence de complexes de ruthénium

Présentée par **Racha ABED ALI ABDINE**
le 02 décembre 2019

Sous la direction des
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Abbreviations

Alloc	allyl chloroformate
Boc	tert-butyloxycarbonyl
BINAP	2,2′-bis(diphenylphosphino)-1,1′-binaphthyl
C	Celsius
cat.	catalyst
conc	concentrated
DABCO	1,4-diazabicyclo[2.2.2]octane
DavePhos	2-Dicyclohexylphosphino-2′-(N,N-dimethylamino)biphenyl
DCE	dichloroethane
DCM	dichloromethane
DEMS	diethoxymethylsilane
DMA	dimethylacetamide
DMAP	4-dimethylaminopyridine
DME	dimethoxyethane
DMF	*N,N*-dimethylformamide
DMSO	dimethylsulfoxide
dppe	1,2-Bis(diphenylphosphino)ethane
dppf	1,1'-Bis(diphenylphosphino)ferrocene
DTBM-SEGPHOS	[4-[5-bis(3,5-di*tert*-butyl-4-methoxyphenyl)phosphanyl-1,3-benzodioxol-4-yl]-1,3-benzodioxol-5-yl]-bis(3,5-di*tert*-butyl-4-methoxyphenyl)phosphane
Et_3N	triethylamine
EDG	Electron donating group
equiv	equivalent
EWG	Electron withdrawing group
GC-MS	gas chromatography–mass spectrometry
HIV	human immunodeficiency viruses
HPLC	high-performance liquid chromatography
L	ligand
m	meta
M	molar
Me-Duphos	(2R,2′R,5R,5′R)-2,2′,5,5′-Tetramethyl-1,1′-(o-phenylene)diphospholane
MPa	megapascal
M^T	Transition metal
NHC	*N*-heterocyclic carbene
NMP	*N*-methylpyrrolidinone
o	ortho
p	para
PG	Protecting group
PyBOX	bis(oxazolyl)pyridine
rt	room temperature
SN	nucleophilic substitution
TFA	Trifluoroacetic acid
THF	tetrahydrofurane
Tol-BINAP	2,2′-Bis(di-*p*-tolylphosphino)-1,1′-binaphthyl
TMEDA	tetramethylethylenediamine
TMS	trimethylsilyl group

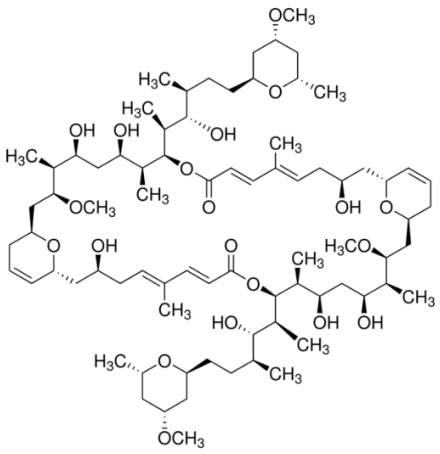
troc	trichloroethyl chloroformate
Xyl-BINAP	2,2'-Bis[di(3,5-xylyl)phosphino]-1,1'-binaphthyl

General introduction

The pioneer discoveries of transition metal complexes have increased the number of synthetic methods in organic chemistry. This evolution has been valued by many Nobel prizes such as Sharpless-Noyori-Knowles's prize for the asymmetric catalysis in 2001, Chauvin-Grubbs-Schrock's prize for the metathesis developpement in 2005 and Heck-Negishi-Suzuki's prize for palladium cross coupling reaction in 2010. More then ever, the progress in organometallic catalysis is still increasing.

Transition metal-catalyzed reactions provide interesting tools for the creation of new bonds and for important transformations. Many reasons led to the success of these reactions: they occurred with an optimal selectivity control (regio-, chemo- and stereoselectivity). In addition, most of the catalytic methods are fitting with the atom economy criterias. These advantages led catalytic reactions to be increasingly employed in total synthesis especially with complicated structures.

For example, Krische's group reported the total synthesis of Swinholide A, a marine sponge with high biological activities (Figure 1).[1] This 44-membered polyketide having 30 chiral centers was synthesized in 15 steps including 5 steps of olefin metathesis, and 5 steps of regio- and stereoselective C-C bonds formation catalyzed by transition metals (such as allylation of a non protected alcohol). Therefore, two thirds of the steps required transition metal to catalyze these coupling reactions. It is worthy to note that the synthesis of Swinholide A, was firstly described by Paterson[2] and Nicolaou[3] groups with respectively 27 and 33 steps. The advantage of this new method is not only in the number of steps but also in the minimal use of protecting groups and non-strategic redox reactions due to the success of the selective coupling reactions.[4]



44-membered polyketide
30 chiral centers

15 steps total synthesis by Krische in 2016 :

-5 steps M^T-catalyzed C-C coupling
-5 steps of olefin metathesis

Figure 1 : structure of Swinholide A.

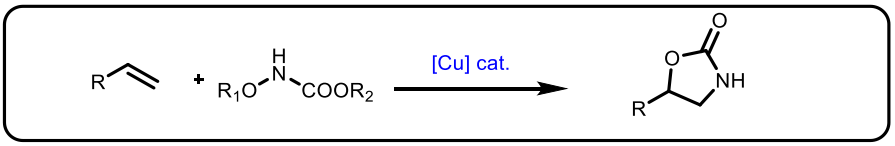
Organometallic catalysis has been in most cases an ecofriendly path for the synthesis of chemical compounds. Despite all the progress, we still need new tools for the selective formation of C-C and C-heteroatom bonds. Hence, it is important to find new economic and selective methods to create molecules through specific bond formation with cheap and low toxic metals.

[1] I. Shin, S. Hong, M. J. Krische, *J. Am. Chem. Soc*. **2016**, 138, 14246.
[2] I. Paterson, K.-S. Yeung, R. A. Ward, J. G. Cumming, J. D. Smith, *J. Am. Chem. Soc*. **1994**, 116, 9391.
[3] K. C. Nicolaou, K. Ajito, A.P. Patron, H. Khatuya, P. K. Richter, P. Bertinato, *J. Am. Chem. Soc*. **1996**, 118, 3059.
[4] To check the rulebook of reaction classification: J. Schwan, M. Christmann, *Chem. Soc. Rev.,* **2018**, 47, 7985.

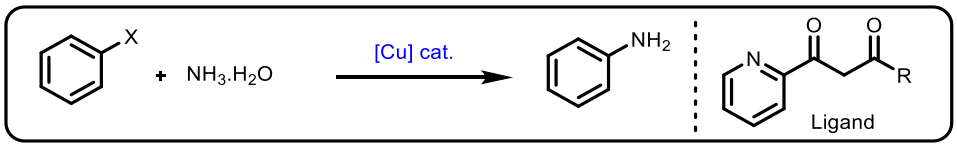
Thus, our laboratory having wide knowledge and expertise in transition metal-catalysis, we were interested in discovering new methods to create selective C-C, C-N, C-O and C-P bonds through the use of two main transition metals: copper and ruthenium.

This thesis manuscript is going to be presented following this plan:

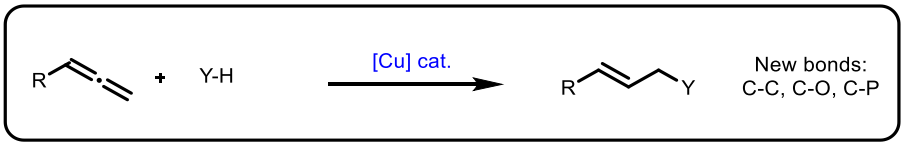
- Chapter 1 presents one-pot alkenes difunctionnalization with amino oxygenated compound to afford oxazolidinone derivatives. This method occurs by using a copper catalytic system.



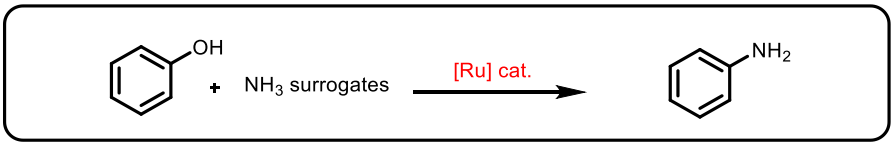
- Chapter 2 illustrates the use of three pyridyl diketones ligands associated to a copper catalyst for the ammonia arylation under mild temperature conditions.



- Chapter 3 focus on the copper-catalyzed hydrofunctionnalization of allenes. With a total atom economy and a free-additional ligand system, these reactions present a valuable tool to create selective C-C, C-O and C-P bonds.



- Chapter 4 introduces the use of ruthenium complexes in order to realize direct amination of phenol on the *ipso*-position without previous transformation or activation of the function – OH.



Chapter I:

Synthesis of oxazolidin-2-one from alkenes catalyzed by copper

Oxazolidin-2-one or 2-oxazolidinone is a heterocyclic compound, in particular a 5-membered ring containing carbonyl function, oxygen and nitrogen atoms (Figure 2, i). A tautomeric form can also be written when the nitrogen is not substituted (Figure 2, ii).

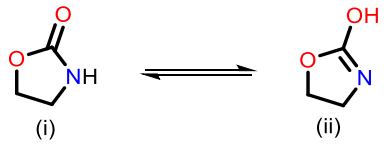


Figure 2 : the structure of oxazolidinone and its tautomer.

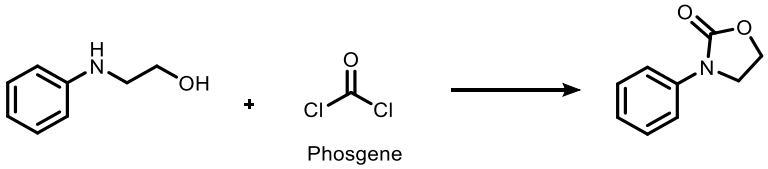
Oxazolidinone and derivatives are widely used as building block in organic chemistry and as key unit for a variety of active and natural products. These moieties gained a particular attention due to their presence in many other fields of chemistry such as pharmaceutical and material sciences.[5]

I. Preparation of Oxazolidin-2-one

Many expedient and efficient methods for the synthesis of oxazolidinone and derivatives were developed in inter- and intramolecular ways. Herein we report the intermolecular methods classified by the nature of the starting materials.

i. From Amino alcohols

In 1891, Phosgene has been used as reagent for the oxazolidinone synthesis.[6] The reaction occurs by double substitution of the chlorine atoms with oxygen and nitrogen atoms (Scheme 1). Phosgene is a very toxic and corrosive gas. It was used during the first world war as chemical weapon and induced more than 80000 deaths. The high toxic property of phosgene remains the main limit to use this synthetic route of the oxazolidinone synthesis.



Scheme 1 : synthesis of N-substituted oxazolidinone by using phosgene.

To avoid using phosgene, Alper and Chouhan replace it by triphosgene (Figure 3), an easy handle solid.[7] They applied this reaction to three different amino alcohols and they obtained successfully the corresponding oxazolidinone.

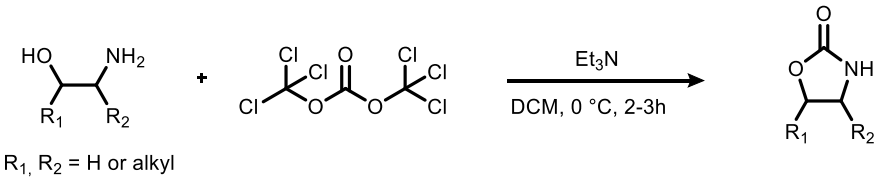
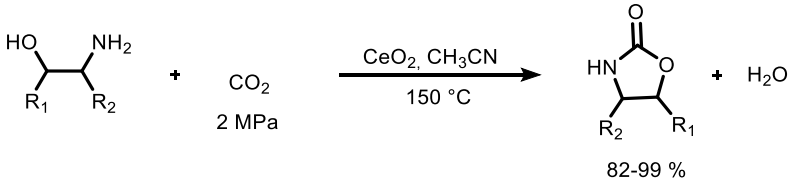


Figure 3 : triphosgene as carbonyl source for the oxazolidinone synthesis.

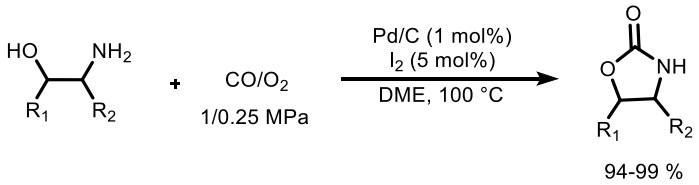
[5] M. E. Dyen, D. Swern, *Chem. Rev*. **1967**, 67, 197.
[6] P. Otto, J. Für, *Prakt. Chem.* **1891**, 44, 15.
[7] G. Chouhan, H. Alper, *J. Org. Chem.* **2009**, 74, 6181.

Carbone dioxide can also promote the cyclization of amino alcohols. Under a pressure of CO_2, this reaction was reported with different catalysts like ammonium fluoride[8], chlorostannoxanes[9] or cerium oxide (Scheme 2)[10]. Water is produced as a byproduct in this reaction.



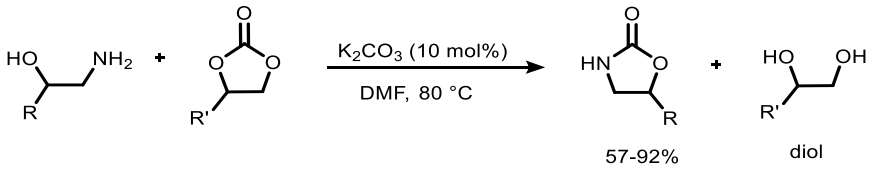
Scheme 2 : oxazolidinone synthesis by using cerium oxide catalyst.

Carbon monoxide have been employed as well for the amino alcohol's cyclocarbonylation[11]. Catalyzed by palladium on carbon and in presence of oxygen, oxazolidinone is obtained in excellent yield at 100 °C (Scheme 3). They used I_2 as promoter to obtain an excellent turnover frequency.



Scheme 3 : palladium catalyzed cyclocarbonylation of amino alcohols.

Cyclic and linear carbonate are used as alternative of carbon monoxide and carbon dioxide to successfully realize the amino alcohols cyclization. In 2007, Xia's group reported the synthesis of oxazolidinone by using dioxolanone and K_2CO_3 as catalyst (Scheme 4).[12] This reaction is carried out at 80 °C in DMF and gives diol as byproduct.

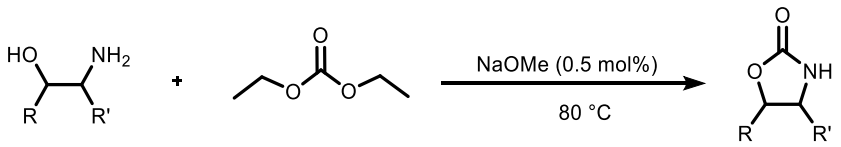


Scheme 4 : oxazolidinone synthesis by using potassium carbonate as catalyst.

Later, Bhanage and coworkers used 15 % of MgO to catalyze the same reaction.[13] They obtained the desired product with good yields after a reaction of amino alcohols with dioxolanone derivatives in ethanol at 80 °C.

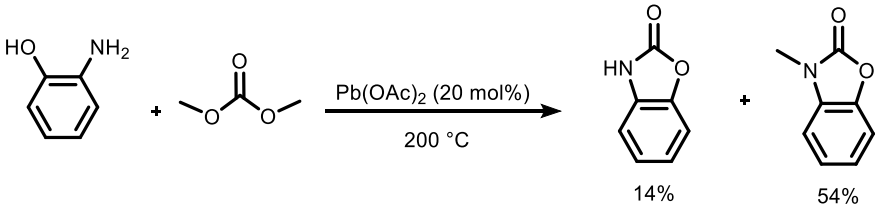
Many catalysts have been used to realize the synthesis of oxazolidinone *via* amino alcohols and linear carbonate. The latter is used in large excess as reagent and solvent in the same time. The first example was patented in 1946.[14] The reaction occurs at 80 °C between amino alcohol and diethyl carbonate and catalyzed by sodium methylate (Scheme 5).

[8] Y. Takada, S. W. Foo, Y. Yamazaki, S. Saito, *RSC Adv*. **2014**, 4, 50851.
[9] S. Pulla, C. M. Felton, Y. Gartia, P. Ramidi, A. Ghosh, *ACS Sustain. Chem. Eng*. **2013**, 1, 309.
[10] M. Tamura, M. Honda, K. Noro, Y. Nakagawa, K. Tomishige, *J. Catal*. **2013**, 305, 191.
[11] F. Li, C. Xia, *J. Catal*. **2004**, 227, 542.
[12] L. Xiao, L. Xu, C. Xia, *Green Chem*. **2007**, 9, 369.
[13] S. R. Jagtap, Y. P. Patil, S.-I. Fujita, M. Arai, B. M. Bhanage, *Appl. Catal. A. Gen*. **2008**, 341, 133.
[14] A. H. Homeyer, *2-Oxazolidone Compounds and Method for Preparing the Same*, **1946**, CA 2,399,188C.



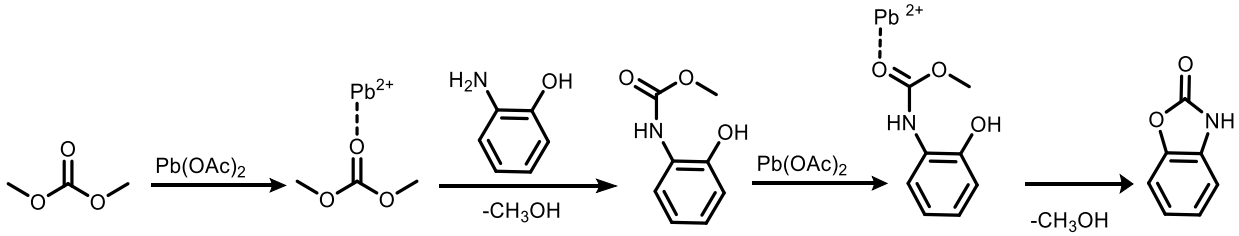
Scheme 5 : synthesis of oxazolidinone from amino alcohols and diethyl carbonate.

In 2001, Ono's group published a novel catalytic system based on 20% of $Pb(OAc)_2$ to realize the carbonylation of *o*-aminophenol with dimethyl carbonate.[15] Only 14% of 2-benzoxazolone were formed whereas the major product was 3-methyl-2-benzoxazolone resulting from the methylation of the first one (Scheme 6). Therefore, in this example the dimethylcarbonate works as carbonylation and methylation agent in the same time.



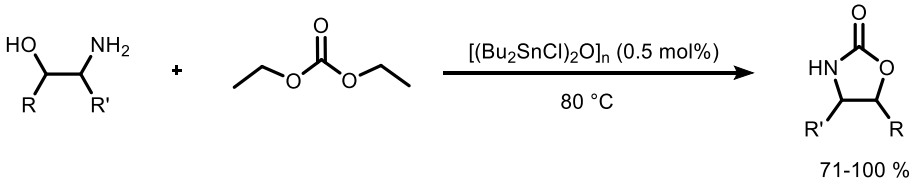
Scheme 6 : Pb-catalyzed synthesis of oxazolidinone.

Pb salt was using as Lewis acid that can increase the polarization of carbonyl function of the dimethyl carbonate by its coordination to the oxygen. Thus, the reaction with the amino alcohols proceeds easily and affords oxazolidinone after double substitution with oxygen and nitrogen atoms (Scheme 7).



Scheme 7 : proposed mechanism for the Pb-catalyzed synthesis of oxazolidinone.

Ten years ago, Munshi's and Růžička's groups reported separately the cyclization of amino alcohols with respectively diethyl carbonate[16] (Scheme 8) and dimethyl carbonate [17] by using tin catalysts.

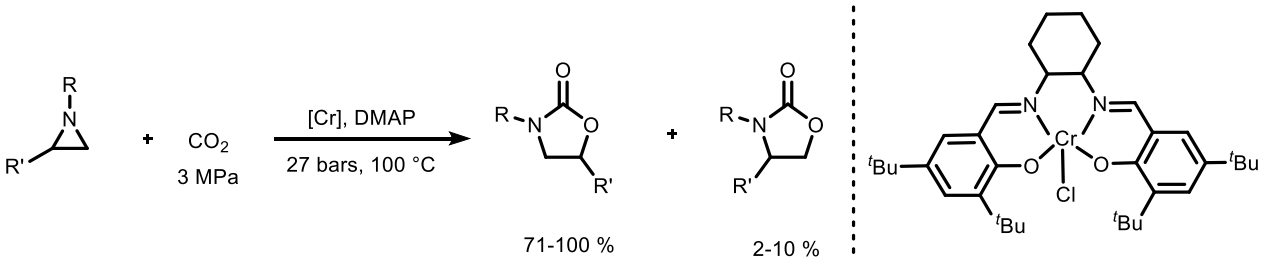


Scheme 8 : Sn-catalyzed synthesis of oxazolidinone.

[15] Y. Fu, T. Baba, Y. Ono, *J. Catal*. **2001**, 197, 91.
[16] S. Pulla, V. Unnikrishnan, P. Ramidi, S. Z. Sullivan, A. Ghosh, J. L. Dallas, P. Munshi, *J. Mol. Catal. Chem.* **2011**, *338*, 33.
[17] T. Weidlich, L. Dušek, B. Vystrčilová, A. Eisner, P. Švec, A. Růžička, *Appl. Organomet. Chem.* **2012**, *26*, 293.

ii. From aziridines

Aziridine proved to be an important intermediate for the oxazolidin-2-one synthesis. This 3-membered ring leads to a 5-membered one after the insertion of CO_2 by using a catalyst. In 2004, Nguyen and Miller used a chromium-salen catalyst associated to DMAP to achieve the coupling of CO_2 with aziridine (Scheme 9).[18]

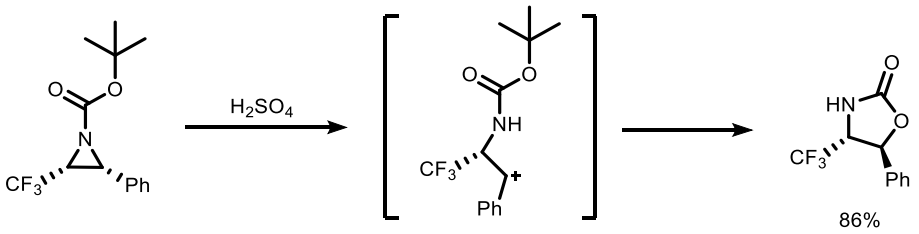


Scheme 9 : synthesis of oxazolidinone by insertion of CO_2 in an aziridine cycle.

In 2014, Lu's group realized the same coupling reaction by using aluminum-salen.[19] This catalyst showed an excellent activity and a high regioselectivity.

To avoid using high pressure like the case of two methods cited above, many papers reported a simple and an efficient approach without the use of CO_2 gas. These reactions occur in intramolecular ways.

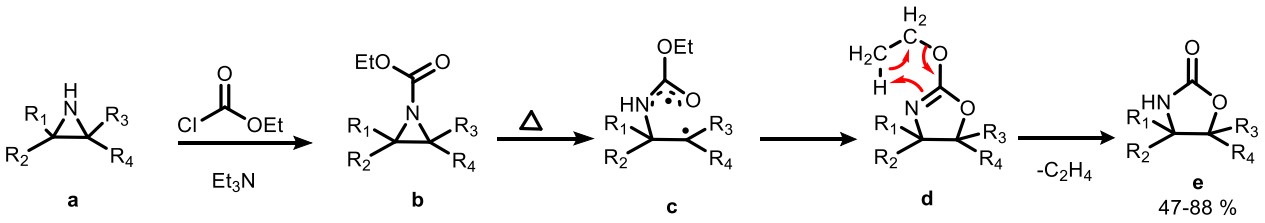
Among these works, Mison and co-workers described in 1989 the isomerization of *N*-protected aziridine by using one of these three promoters: sodium iodide, heating or Brönsted acid.[20] For instance, in a concentrated solution of sulfuric acid, the corresponding oxazolidinone is formed with a good yield (Scheme 10). The presence of trifluoromethyl group on the aziridine leads to obtain a regioselective product.



Scheme 10 : sulfuric acid promoting the rearrangement of aziridine.

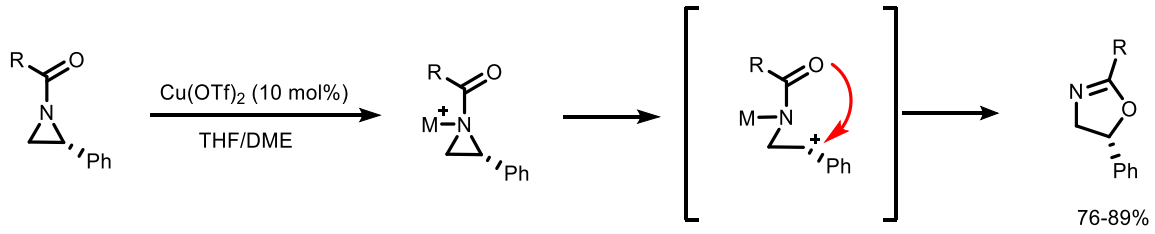
Two years later, Thomson's group described the synthesis of oxazolidinone *via* an aziridine rearrangement (Scheme 11).[21] The simple aziridine (**a**) is converted to *N*-ethoxycarbonyl aziridine (**b**) by reaction with ethyl chloroformate in presence of a base. Then, an isomerization takes place under thermal conditions, *via* formation of diradicals species (**c**). This step led to the insertion of the CO_2 moiety in the cycle and provide the 2-ethoxy-4,5-dihydrooxazole (**d**) which can undergo a thermal elimination of 1 equiv of ethylene and thus affords the corresponding oxazolidinone (**e**).

[18] A. W. Miller, S. T. Nguyen, *Org. Lett.* **2004**, *6*, 2301.
[19] W.-M. Ren, Y. Liu, X.-B. Lu, *J. Org. Chem.* **2014**, *79*, 9771.
[20] K. Quinze, A. Laurent, P. Mison, *J. Fluorine. Chem.* **1989**, 44, 233.
[21] M. R. Banks, J. I. G. Cadogan, I. Gosney, P. K. G. Hodgson, D. E. Thomson, *J. Chem. Soc. Perkin. Trans*. **1991**, 961.



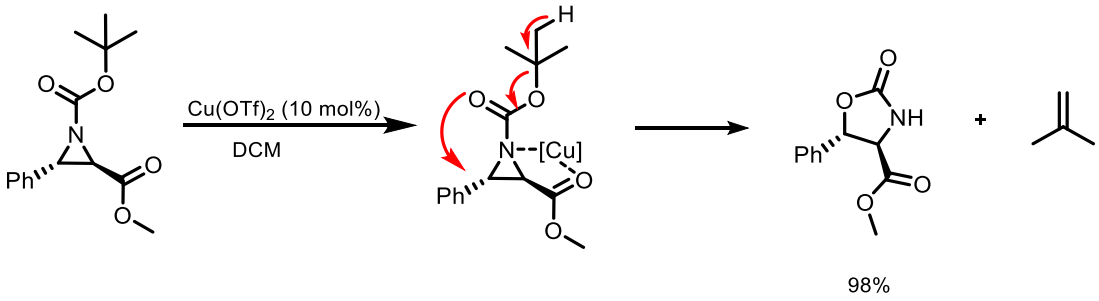
Scheme 11 : proposed mechanism for the aziridine rearrangement intiated by thermal condition.

In 1998, Lectka's group showed the effect of azaphile Lewis acid in presence of *N*-Acylaziridine (Scheme 12).[22] Catalytic amount of metal triflate like Cu, Zn or Sn was used, then the metal coordinate to the nitrogen atom. This coordination enhances the nucleophilicity of the acetyl oxygen to attack then the incipient carbocation formed due to the same coordination. The rate of this catalyzed rearrangement increased with the presence of electron-donating group on the aziridine ring. The oxazoline was obtained in a good to excellent yield.



Scheme 12 : copper-catalyzed rearrangement of aziridine on oxazoline.

One year later, Vecchione and Tomasin reported *N-tert*-Butoxycarbonyl aziridine rearrangement in presence of 10% of $Cu(OTf)_2$.[23] This Lewis acid coordinate the nitrogen atom, and chelates in the same time the carbonyl oxygen of an ester substituting in the C_2 position (Scheme 13). The rearrangement proceeds similarly to the one cited above with elimination of 1 equiv of isobutene, to produce oxazolidinone with a complete stereo- and regioselectivity.



Scheme 13 : Lewis acid-catalyzed the rearrangement of *N*-tert-Butoxycarbonyl aziridine.

Nowadays, due to its simplicity and efficiency, this kind of rearrangement is used after as common method to synthesize oxazolidinone through *N*-activated aziridine and in presence a catalytic amount of simple and cheap Lewis acid.[24]

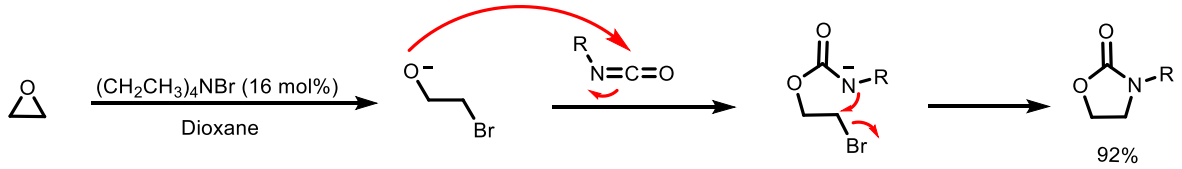
[22] D. Ferraris, W. J. Drury, C. Cox, T. Leckta, *J. Org. Chem*. **1998**, 63, 4568.

[23] C. Tomasini, A. Vecchione. *Org. Lett.,* **1999**, 1, 2153.

[24] Some examples : a) Z. Lu, Y. Zhang, W. D. Wulff, *J. Am. Chem. Soc*. **2007**, 129, 7185. b) I. Tirotta, N. L. Fifer, J. Eakins, C. A. Hutton, *Tetrahedron. Lett*. **2013**, 54, 618. c) G. Righi, G. Scotti, F. Caruso, M. Rossi, F. Mecozzi, R. Antonioletti, R. Pelagalli, *Tetrahedron. Lett*. **2013**, 69, 9557.

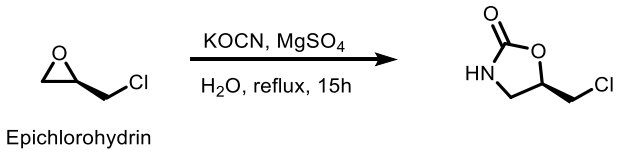
iii. From epoxides

Another 3-membered ring used for the oxazolidinone synthesis is the epoxide by a reaction with isocyanate (Scheme 14).[25] The presence of trialkyl ammonium halogen opens the epoxide and form the corresponding alkoxide. Then, the latter attacks the isocyanate carbonyl and yields an amide anion, which does a substitution with the halogen to form the oxazolidinone cycle. The main drawback of this method is the toxicity of the isocyanate.



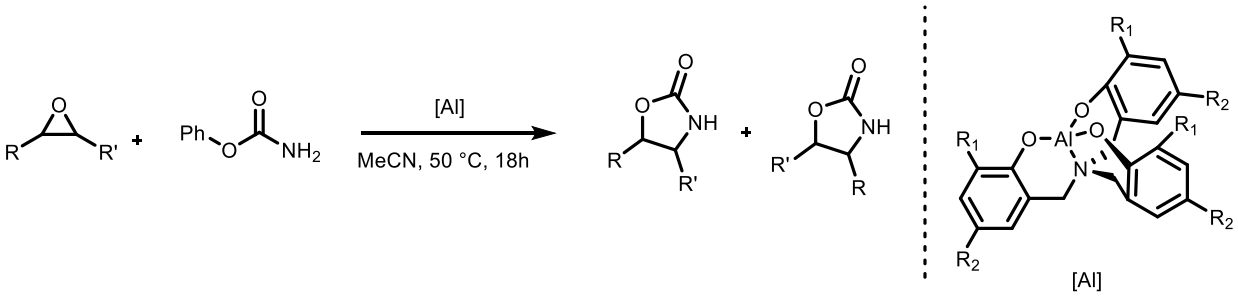
Scheme 14 : synthesis of oxazolidinone from epoxide.

In 2011, Madhusudhan's group[26] reported the synthesis of oxazolidinone from epichlorohydrin and potassium cyanate. This reaction is carried out in presence of $MgSO_4$ in a reflux of water (Scheme 15).



Scheme 15 : synthesis of oxazolidinone from epichlorohydrin.

Other method to transform the epoxide to oxazolidinone, consists in using carbamate as nucleophile to open the cycle. This method was developed by Kleij's group in 2015 in order to synthesize a scope of urea by a single step after the synthesis of oxazolidinone.[27] Through an aluminium catalysis, they synthesized a wide variety of oxazolidinone derivatives by using phenyl carbamate (Scheme 16). The main drawback of this method is the regioselectivity of the nucleophilic attack, thus providing in most of the cases a mixture of two regioisomers.



Scheme 16 : oxazolidinone synthesis from epoxide catalyzed by aluminium.

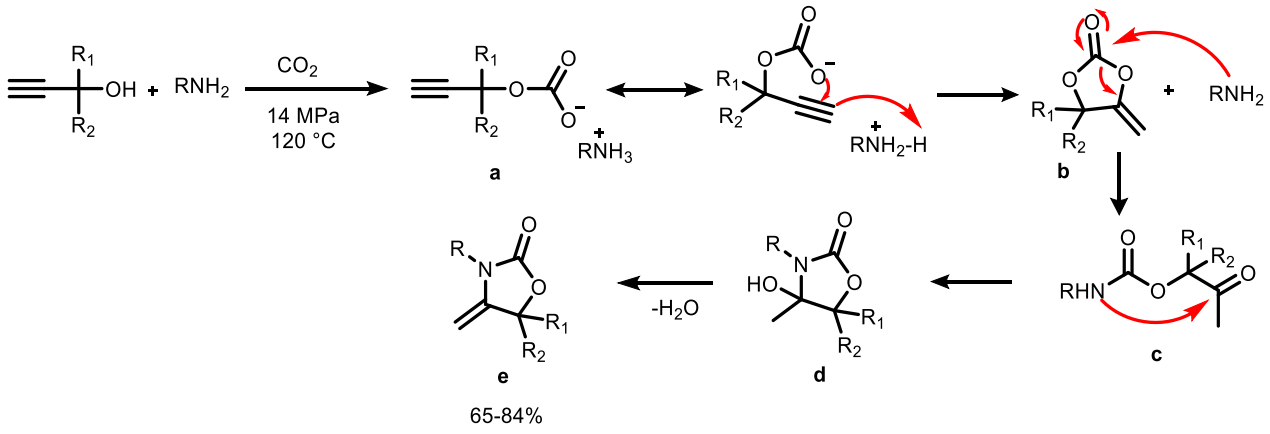
iv. From propargylic alcohols and amines

As an excellent one-carbon source, CO_2 have been used widely for oxazolidinone synthesis from propargylic compounds.

Under supercritical condition and without catalyst, propargylic alcohols react with primary amine and carbon dioxide (Scheme 17). It affords the ammonium carbonate **a**, which undergoes a cyclization

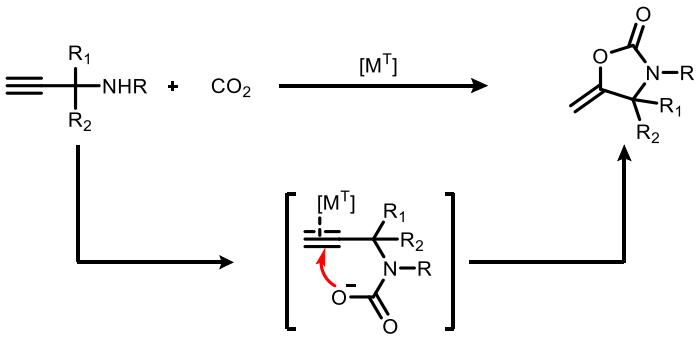
[25] G. P. Speranza, W. J. Peppel, *J. Org. Chem.* **1958**, *23*, 1922.
[26] T. Rajesh, P. S. Reddy, M. Manidhar, M. Vijayalakshami, G. Madhusudhan, *J. Chem.* **2011**, 8, 1417.
[27] V. Laserna, W. Guo, A. W. Kleij, *Adv. Synth. Catal.* **2015**, 357, 2849.

to afford α-methylene dioxolanone **b** and to regenerate the primary amine. The latter attacks then the carbonyl group of the cyclic carbonate and form the corresponding carbamate. An intramolecular reaction occurs by the attack of the nitrogen on the ketone carbonyl of **c**, yielding the 4-hydroxy oxazolidinone **d**. A simple hydration step affords efficiently the corresponding 4-methyleneoxazolidinone **e**.[28]



Scheme 17 : synthesis of oxazolidinone from propargylic alcohol and primary amine.

As well propargylic amine was used widely with CO_2 for the same goal. Many transition metals such as silver, copper, gold, palladium, ruthenium and zinc have been used to catalyze the insertion of CO_2 and then the cyclization.[29] In these cited examples, the first step is the carboxylation of the amine yielding the carbamate. Then, the metal works commonly as Lewis acid which can coordinate the triple bonds and thus enhances the reactivity with the carbamate to afford the cyclic product (Scheme 18).

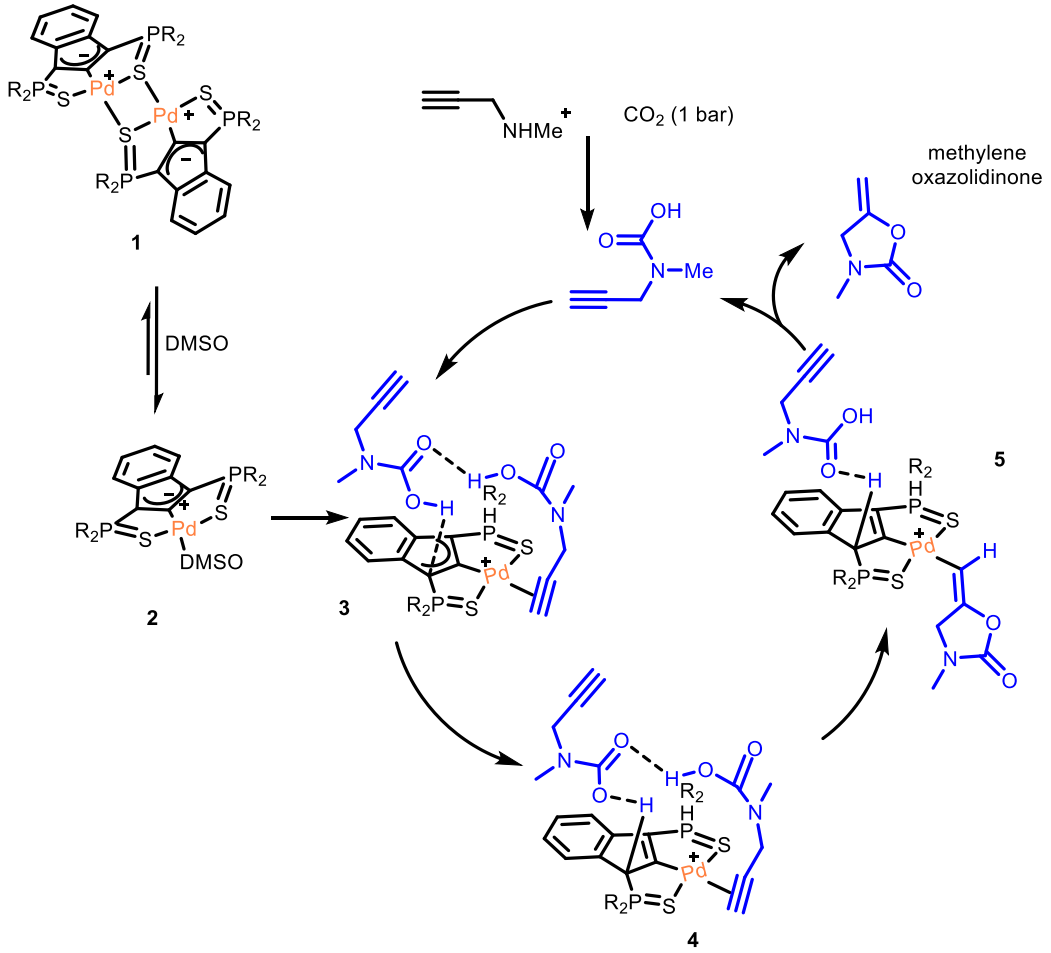


Scheme 18 : metal transition-catalyzed the carboxylative cyclization of propargylic amine.

For example, Martin-Vaca and Bourissou reported in 2017 the synthesis of 2-oxazolidinone through a carboxylative cyclization of propargylamine promoted by indenediide SCS-palladium pincer complex.[30] A serie of oxazolidinones was obtained with good to excellent yields thanks to a metal-ligand cooperativity. Due to the high polarity of DMSO, the latter split the dimer **1** and coordinate to the palladium, thereby affording a labile adduct **2** (Scheme 19). The carbamic acid produced by the carboxylation of propargylic amine can replace the DMSO, and coordinate to palladium by the triple bond, and in the same time it interact by hydrogen bonding with another molecule of carbamic acid. This one interacts by its acidic proton with the SCS ligand **3**. It then transfers this acidic proton to the ligand backbone **4**. Then, the activated triple bond undergoes a nucleophilic attack from the acid of the same molecule to yield the cyclic ring which is bonding to palladium **5**. The remaining carbamic

[28] J. X. Xu, J. W. Zhao, Z. B. Jia, *Chin. Chem. Lett.* **2011**, *22*, 1063.
[29] Z. Zhang, J.-H. Ye, D.-S. Wu, Y.-Q. Zhou, D.-G. Yu, *Chem. Asian. J.* **2018**, 13, 2292.
[30] P. Brunel, J. Monot, C. E. Kefalidis, L. Maron, B. Martin-Vaca, D. Bourissou, *ACS Catal.* **2017**, 7, 2652.

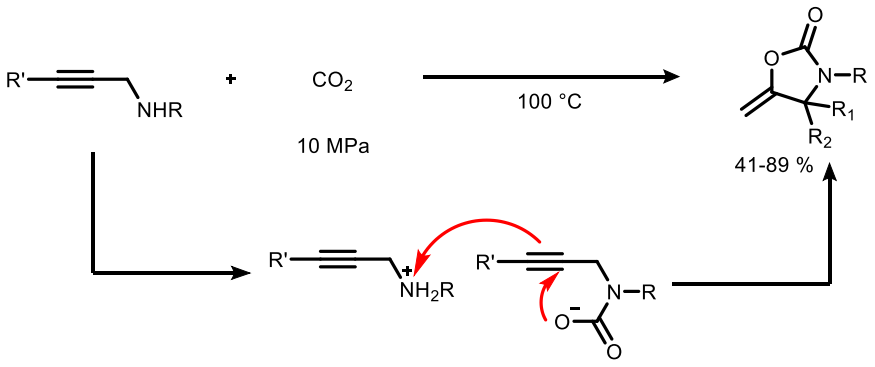
acid is weakly hydrogen bonded to the ligand, and can promote a back transfer of a proton from the ligand to the cyclic compound releasing the methylene oxazolidinone and thus regenerating the indenediide pincer complex that can undergo another catalytic cycle.



Scheme 19 : palladium-ligand cooperative catalysis for oxazolidinone synthesis.

Aluminium as a post transition metal has also been used for the carboxylative cyclization reaction of propargylic amine.[31] Furthermore, metal-free methods have been developed for the reaction of propargylic amine with CO_2, for example by using a base which can play an important role for the activation of CO_2. Supercritical CO_2 was reported by Ikariya's group for the oxazolidinone synthesis without need for a metal neither a base. The amine itself reacts with carbone dioxide, and the ammonium cation resulting from this reaction acts for the activation of the triple bonds (Scheme 20).[32]

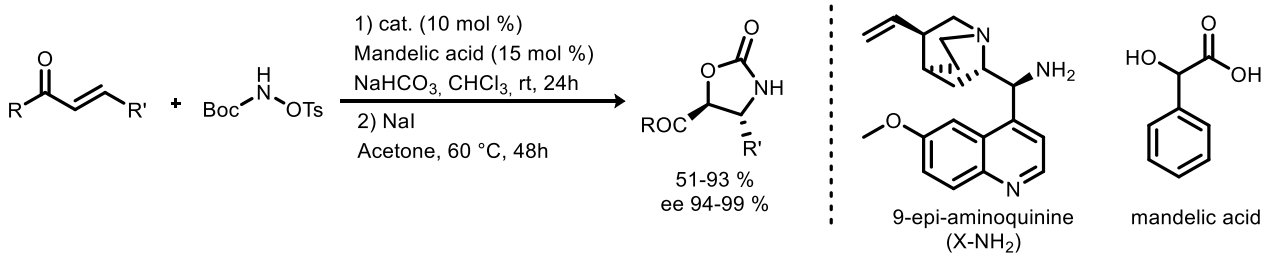
[31] R. Maggi, C. Bertolotti, E. Orlandini, C. Oro, G. Sartori, M. Selva, *Tetrahedron Lett.* **2007**, *48*, 2131–2134.
[32] Y. Kayaki, M. Yamamoto, T. Suzuki, T. Ikariya, *Green Chem*. **2006**, 8, 1019.



Scheme 20 : synthesis of oxazolidinone from propargylic amine in presence of supercritical CO_2.

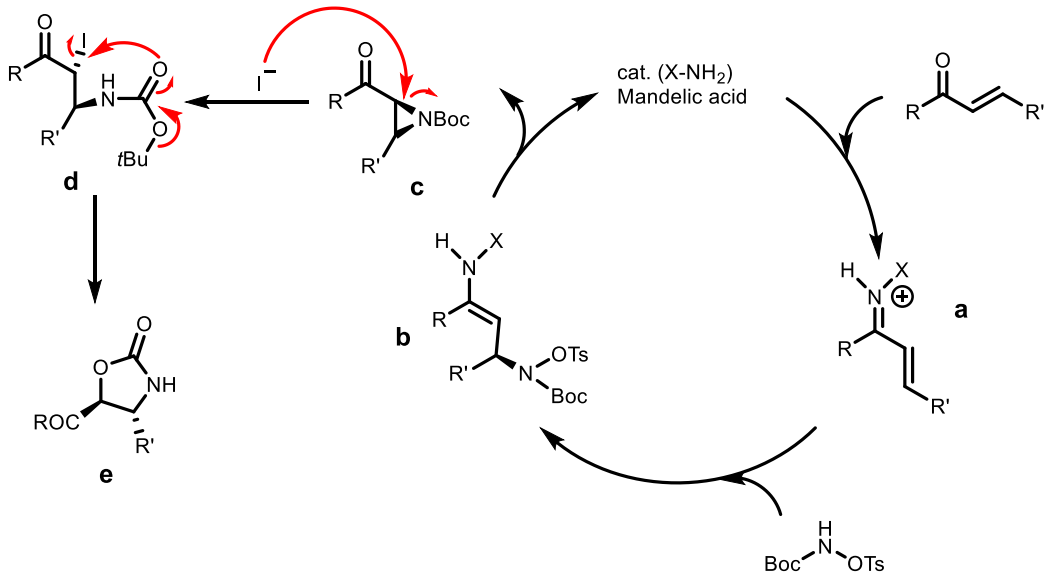
v. From alkenes

In 2012, Jørgensen and coworkers described an organocatalytic synthesis of oxazolidinone from enone derivatives (Scheme 21).[33] Following the enone aziridination reaction developed for the first time by Melchiorre[34], the authors realized the aminocatalyzed aziridine: after condensation of the organocatlyst (9-epi-aminoquinine) with the enone, an iminium ion specie (**a**) is formed, which undergoes a nucleophilic attack from the protected hydroxylamine (**b**) followed by a ring closure and a hydrolysis affording thereby the *N*-Boc-aziridine (**c**) and releasing the aminocatalyst. The treatment of this aziridine with NaI at 60 °C for 48 hours provide the corresponding oxazolidinone. This step occurs through a double SN_2, the first one by the attack of iodide ion on the α carbonyl position to open the aziridine and yielding (**d**) and the second one by an intramolecular *O*-alkylation to form the final 5-membered ring cycle (**e**). This reaction condition was applied on several β-substituted enone, and gave the corresponding oxazolidinone in moderate to excellent yields.



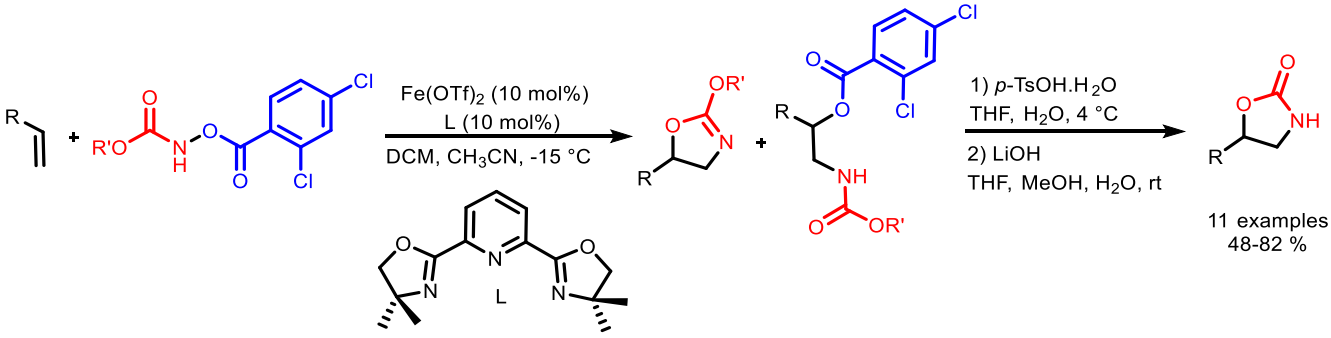
[33] D. C. Cruz, P. A. Sanchez-Murcia, K. A. Jørgensen, *Chem. Commun.*, **2012**, 48, 6112.

[34] F. Pesciaioli, F. De Vincentiis, P. Galzerano, G. Bencivenni, G. Bartoli, A. Mazzanti and P. Melchiorre, *Angew. Chem., Int. Ed.*, **2008**, 47, 8703.



Scheme 21 : synthesis of oxazolidinone from enone.

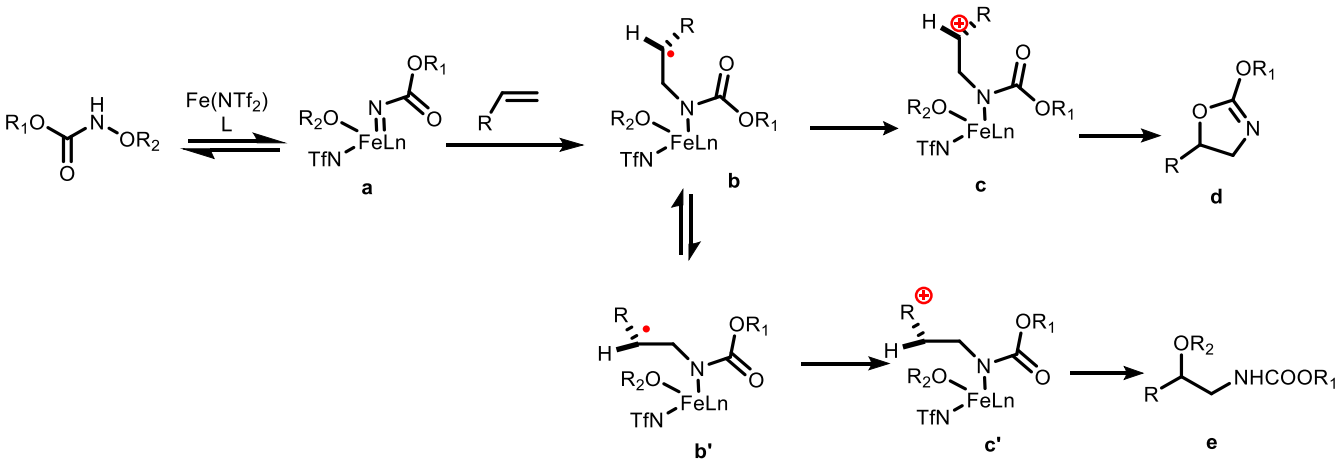
Later, Xu's group developed in 2014 an olefin amino-oxygenation by using iron based catalytic system (Scheme 22).[35] This intermolecular reaction occurs between a functionalized hydroxylamine and an alkene catalyzed by an iron (II) associated to a bisoxazoline PyBOX ligand. It affords a mixture of alkoxyl oxazoline and protected amino alcohol in a good to excellent yield. Then, both of these two products can undergo a hydrolytic condition to afford in some cases oxazolidinone in a good yield. It is necessary to use an electrophilic amine to get a high reactivity.



Scheme 22 : synthesis of oxazolidinone in two steps from alkenes.

The reaction takes place through a radical mechanism (Scheme 23). The iron complex cleaves the N-O bonds of the amination reagent and forms an iron nitrenoid specie **a**. This one leads to a radical amination of the alkene, affording two radical conformers **b** and **b'**, which are in equilibrium. Alternatively, **b** can be oxidized by the iron to form the carbocation **c**, which is attacked directly by the carbonyl group to afford the oxazoline **d**. Also, **b'** undergoes an oxidation, followed by a transfer of the carboxylate to provide the corresponding amino alcohol **e**.

[35] a) D.-F. Lu, C.-L. Zhu, Z.-X. Jia, H. Xu, *J. Am. Chem. Soc*. **2014**, 136, 13186. b) C.-L. Zhu, D.-F. Lu, J. D. Sears, Z.-X. Jia, H. Xu, *Synthesis* **2016**, 48, 3031.

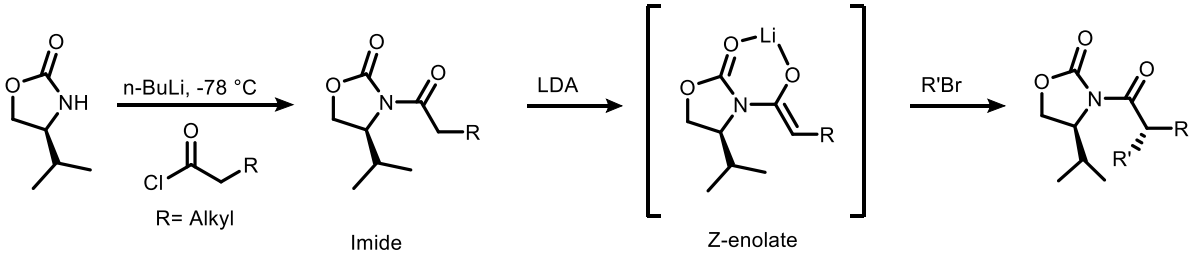


Scheme 23 : radical mechanism for the reaction of alkenes with the electrophilic amine.

II. Application of oxazolidinone

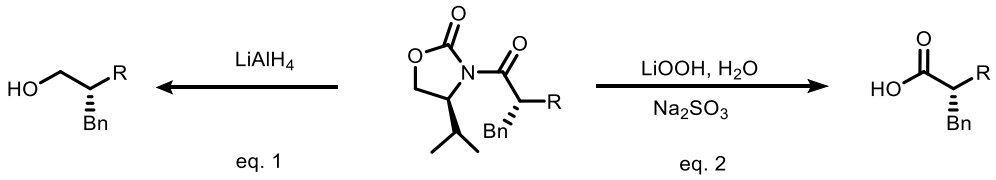
a. Chiral auxiliaries

Oxazolidinone is an important compound in organic chemistry, particulary when the group of David Evans introduced it as chiral auxiliary in asymmetric synthesis[36] for the enantioselective alkylation, Diels-Alder and aldol reactions.[37] For example, chiral oxazolidinone is acylated with an acid chloride to form the corresponding imide (Scheme 24). Then, a strong base can deprotonate the α position to form selectively the *Z*-enolate which undergoes a stereoselective alkylation with an alkyl halide.[38]



Scheme 24 : enantioselective alkylation by using chiral auxiliary.

To remove an oxazolidinone moiety acting as chiral auxiliary, various methods have been developed and can be employed to obtain different functional groups. For example, a reductive cleavage with $LiAlH_4$ produces the corresponding chiral alcohol[38] (Scheme 25, eq. 1). While, under basic conditions the hydrolysis with LiOOH leads to the formation of the chiral carboxylic acid[39] (Scheme 25, eq. 2).



Scheme 25 : cleavage of oxazolidinone.

[36] Y. Gnas, F. Glorius, *Synthesis*, **2006**, 12, 1899.

[37] Chiral auxiliaries are enantiomerically pure compounds linked to a molecule and influence the stereochemistry of a reaction.

[38] D. A. Evans, M. D. Ennis, D. J. Mathre, *J. Am. Chem. Soc.* **1982**, *104*, 1737.

[39] D. A. Evans, T. C. Britton, J. A. Ellman, *Tetrahedron Lett*. **1987**, 28, 6141.

b. Drugs

Oxazolidinones are also used as drugs and bioactive intermediates. Many compounds bearing this moiety, showed a high antibacterial property like Furaltadone[40], Furazolidone[41], Methoxadone[5] (Figure 4).

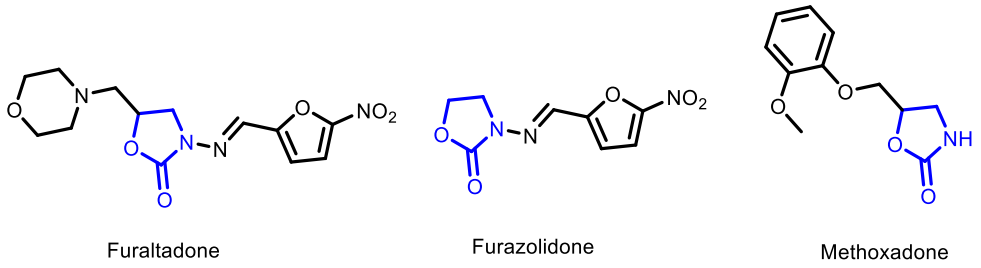


Figure 4 : some examples of oxazolidinone antibacterial reagents.

In 1996, Upjohn company published a study for a structure-activity relationship of oxazolidinone antibacterial agents.[42] This study led to discover Linezolid, an antibiotic marketed since 2000 for the treatment of the infections caused by gram-positive bacteria.[43] Since, similar drugs have been developed such as Tedizolid[44] for the treatment of skin infections and Zolmitriptan[45] for the acute treatment of migraines (Figure 3).

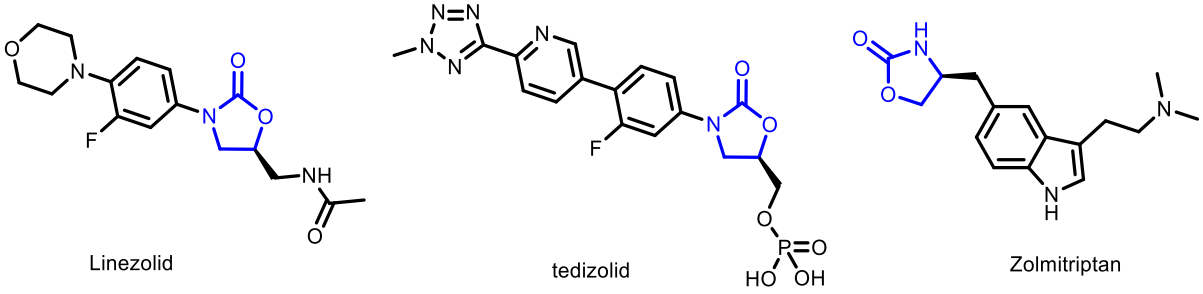


Figure 5 : oxazolidinones with interesting properties.

In 2007, another bio-active molecule containing oxazolidinone skeleton has been discovered: Rivaroxaban, an anticoagulant drug patented by Bayer[46] and used to treat the blood clots (Figure 6).

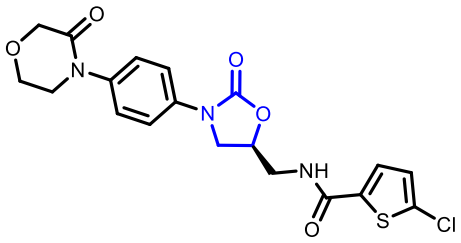


Figure 6 : structure of Rivaroxaban.

[40] W. R. McCabe, J. C. Davis, B. R. Andersen, G. Gee Jackson, *N. Engl. J. Med.,* **1960**, 263, 927.
[41] C. H. Domermuth, *Avian Diseases*. **1958**, 2, 442.
[42] S. J. Brickner, D. K. Hutchinson, M. R. Barbachyn, P. R. Manninen, D. A. Ulanowicz, S. A. Garmon, K. C. Grega, S. K. Hendges, D. S. Toops, C. W. Ford, et al., *J. Med. Chem.* **1996**, *39*, 673–679.
[43] K. L. Leach, S. J. Brickner,M. C. Noe, P.F. Miller, *Ann. N.Y. Acad. Sci*, **2011**, 1222, 49.
[44] G. J. Moran, E. Fang, G. R. Corey, A. F. Das, C. De Anda, P. Prokocimer, *Lancet, Infect. Dis*. **2014**, 14, 696.
[45] K. J. Palmer, C. M. Spencer, *CNS drugs*, **1997**, 7, 468.
[46] A. Straub, T. Lampe, J. Pohlmann, S. Röhrig, E. Perzborn, K.-H. Schlemmer, J. Pernerstorfer, *Substituted Oxazolidinones and Their Use in the Field of Blood Coagulation*, **2007**, US 7,157,456 B2.

Since all these pioneer discoveries, oxazolidinone became an interesting moiety for the medical research area.[47] For example, Gayen and coworkers reported recently the importance of the oxazolidinone for potential HIV-1 protease inhibitors (Figure 7).[48]

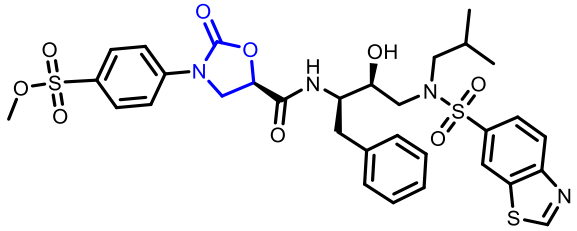


Figure 7 : one of the potential HIV-1 protease inhibitors.

c. Polymer

Another application field of oxazolidinone compounds is polymer science. Different patents reported the importance of oxazolidinone skeleton presence in polymers. Oxazolidinone give the polymers some valuable properties like the resistance in fibers[49] and coating.[50] An important example of a monomer bearing oxazolidinone is the *N*-vinyl-2-oxazolidinone (Figure 8). Due to its low toxicity and viscosity, this compound showed to be a good solvent reagent for the coating composition.[51]

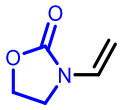
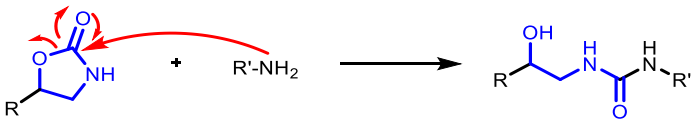


Figure 8 : *N*-vinyl-2-oxazolidinone.

In 1993, Mizuguchi and coworkers reported the replacement of isocyanate by oxazolidinone moiety for the synthesis of polyurea.[52] As isocyante is a toxic composite, the replacement of the latter is considered as a very valuable step. Thus, oxazolidinone can respond to this activity by a ring opening under the attack of a nucleophile like an amine to yield urea monomer (Scheme 26).



Scheme 26 : illustration of the ring opening of oxazolidinone with an amine to form urea.

d. Electrochemistry

Oxazolidinone also showed some application in electochemistry. For instance, Lemordant's group showed that *N*-methyl-2-oxazolidinone could be an electrolyte for the lithium battery in the presence of ethylene carbonate or dimethyl carbonate (Figure 9).[53]

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[47] T. A. Mukhtar, G. D. Wright, *Chem. Rev*. **2005**, 105, 529.

[48] S. A. Amin, N. Adhikari, S. Bhargava, T. Jha, S. Gayen, *SAR QSAR Environ. Res.* **2018**, *29*, 385–408.

[49] S. A. Murdock, T. G. Traylor, T. B. Lefferdink, Graft Polymers Comprised of Mixtures of Vinyl Pyridine Monomers and Certain Monomeric Sulfonic Acid Compounds on N-Vinyl-3-Morpholine Polymer Substrates, Improved Acrylonitrile Polymer Compositions Obtainable *Therewith, and Method of Preparation*, **1962**, US 3, 026, 287 A.

[50] J. A. Clarke, Oxazolidinone-Containing Epoxy Resins and Process for Their Preparation, **1972**, US 3,676,397 A.

[51] J. G. Green, D. G. Hunt, *N-Vinyl-2-Oxazolidinones as Reactives Diluents in Actinic Radiation Curable Coatings*, **1988**, US 4, 774, 307 A.

[52] T. Ishii, H. Nojiri, M. Yamada, R. Mizuguchi, *Thermosetting Resinous Composition Containing Polyfunctional Oxazolidinone Component and Polyamine Component*, **1993**, EP 0, 530, 812 A1.

[53] L. Gzara, A. Chagnes, B. Carré, M. Dhahbi, D. Lemordant, *J. Power Sources* **2006**, *156*, 634

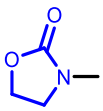


Figure 9 : *N*-methyl-2-oxazolidinone.

III. Objective and results

1. Introduction

- Original study: Direct hydroamination of terpenes

Terpene is a family of organic compounds produced by plants. The most known molecules from this family are α-pinene and β-pinene which are extracted from turpentine oil (350k tons/year), and the limonene existing in the citrus (30k tons/year).[54] Another example of terpene is the myrcene, an important component of the essential oil of different plants like cannabis and pine (Figure 10).

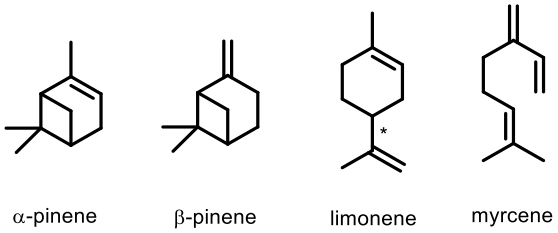


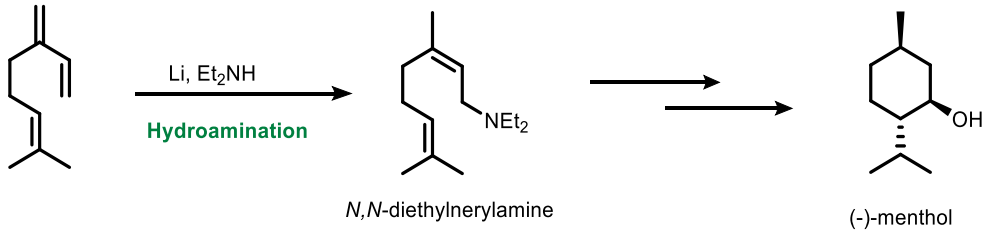
Figure 10 : principal terpenes.

Terpene compounds are composed exclusively of carbon and hydrogen atoms and contain at least one double bond. The latest one can serve as target for the functionalization of these compounds.

Our main objective was to create a new C-N bond by introducing nitrogen atom on simple and accessible terpenes. Thus, we can valorize this type of compounds, which are mainly in their natural form without a valuable interest, useless or considered in some cases as waste.

In this initial project, we planned to produce the corresponding amines that could have many interests and applications in several fields like pharmaceutical industry, or material chemistry. To illustrate this, we can cite the case of myrcene compound. In 1980, myrcene was succefully converted to *N,N*-diethylnerylamine by a hydroamination reaction[55] (Scheme 27). The reaction occurs through lithium-catalyzed addition of diethylamine. This allylic amine was used for an asymmetric synthesis in Takasago process to produce 3k tons per year of the enantioselective (-)-Menthol.[56] This method became the second major commercial route to (-)-menthol. This molecule has an inflammatory and an antiviral property, it is also used to relieve minor irritation of the throat. It works as well as local anesthetic.

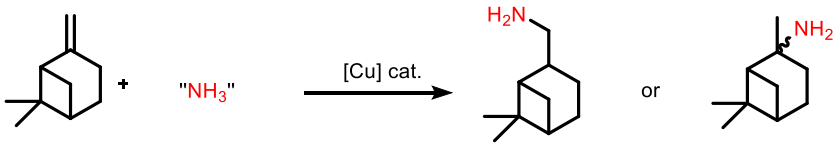
[54] P. Gallezot. *Green Chem.,* **2007**, 9, 295.
[55] K. Takabe, T. Katagiri, J. Tanaka, T. Fujita, S. Wata-nabe, K. Suga, *Org. Synth*. **1989**, 67, 44.
[56] R. Noyori, *Angew. Chem. Int. Ed*. **2002**, 41, 2008.



Scheme 27 : synthesis route of (-)-menthol *via* myrcene by Takasago.

Alkenes hydroaminations have been studied widely in the last decades. Intra- and intermolecular hydroamination were realized with the presence of catalyst such as alkali[57], rare-earth, and transition metals[58,59] or with metal-free conditions through the replacement of the metal by an organocatalyst, Brönsted acid…[59]

Despite the efficiency of some of these methods, there is not in the literature any selective and compatible system for terpenes, using low cost and low toxicity catalyst and yielding the corresponding primary amine. Our aim was to realize the terpenes hydroamination catalyzed by cheap and abundant metal like copper and by using a simple amine transfer reagent to produce the corresponding primary amine (Scheme 28).

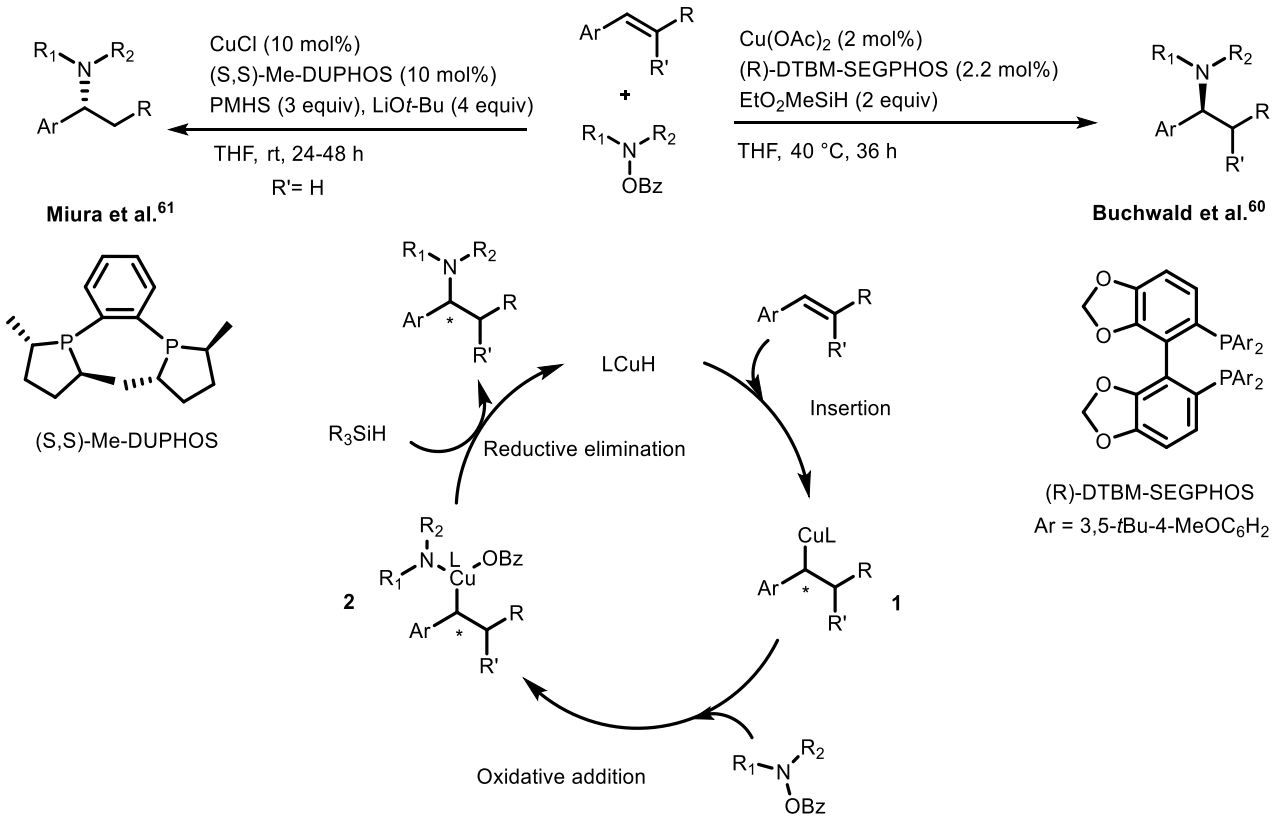


Scheme 28 : hydroamination of β-pinene.

- State of the art

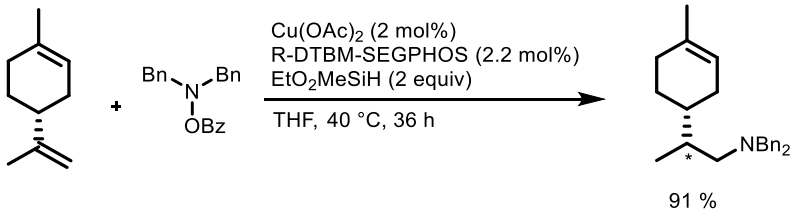
In 2013, the groups of Buchwald[60] and Miura[61] realized separately the hydroamination of alkenes in an umpolung amination approach, with hydroxylamine ester as electrophilic source of amine. They used in the both methods copper salts associated to a chiral diphosphine ligand, and hydride source to generate *in situ* copper hydride [LCuH] which is the catalytic active species (Scheme 29). The insertion of the alkene into the copper hydride specie yields the complex **1**, which undergoes an oxidative addition of the hydroxylamine ester to afford the intermediate **2**. Then, a reductive elimination step occurs in the presence of hydride source to release the corresponding aminated product and the catalytic specie.

[57] T. Fujita, K. Suga, S. Watanabe, *Aust. J. Chem.* **1974**, 27, 531.
[58] L. Huang, M. Arndt, K. Gooßen, H. Heydt, L. J. Gooßen, *Chem. Rev*. **2015**, 115, 2596.
[59] E. Bernoud, C. Lepori, M. Mellah, E. Schulz, J. Hannedouche, *Catal. Sci. Technol*, **2015**, 5, 2017.
[60] S. Zhu, N. Niljianskul and S. L. Buchwald, *J. Am. Chem. Soc.*, **2013**, 135, 15746.
[61] Y. Miki, K. Hirano, T. Satoh and M. Miura, *Angew. Chem., Int. Ed*., **2013**, 52, 10830.



Scheme 29 : hydroamination of alkenes using copper hydride as catalytic system.

To be sure that we are able to form *in-situ* copper hydride species, we started by reproducing Buchwald's conditions with limonene.[62] Using 2 mol% of copper(II) acetate, 2.2 mol% of (R)-DTBM-SEGPHOS and 2 equiv of diethoxymethylsilane as hydride source in THF, we realized the reaction between (R)-limonene and *O*-benzoyl-*N*,*N*-dibenzylhydroxylamine at 40 °C. After 36 hours of reaction we obtained selectively the corresponding tertiary amine in excellent yield, similar to the published results, *via* an anti-Markovnikov addition (Scheme 30).



Scheme 30 : hydroamination of (R)-limonene.

Inspired by these works, we aimed to find a simple copper catalyzed method for the terpenes hydroamination with simple protected electrophilic amines to afford terpenes bearing NH_2 function.

2. Synthesis of electrophilic amines

To begin our study, we started by the synthesis of the amine source. We looked to perpare a serie of electrophilic secondary amine protected with an easy removable group like Boc or Alloc (Figure 11). These electrophilic amines could play the role of NH_3 surrogate.

[62] S. Zhu, S. L. Buchwald, *J. Am. Chem. Soc*. **2014**, 136, 15913.

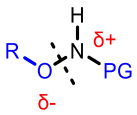
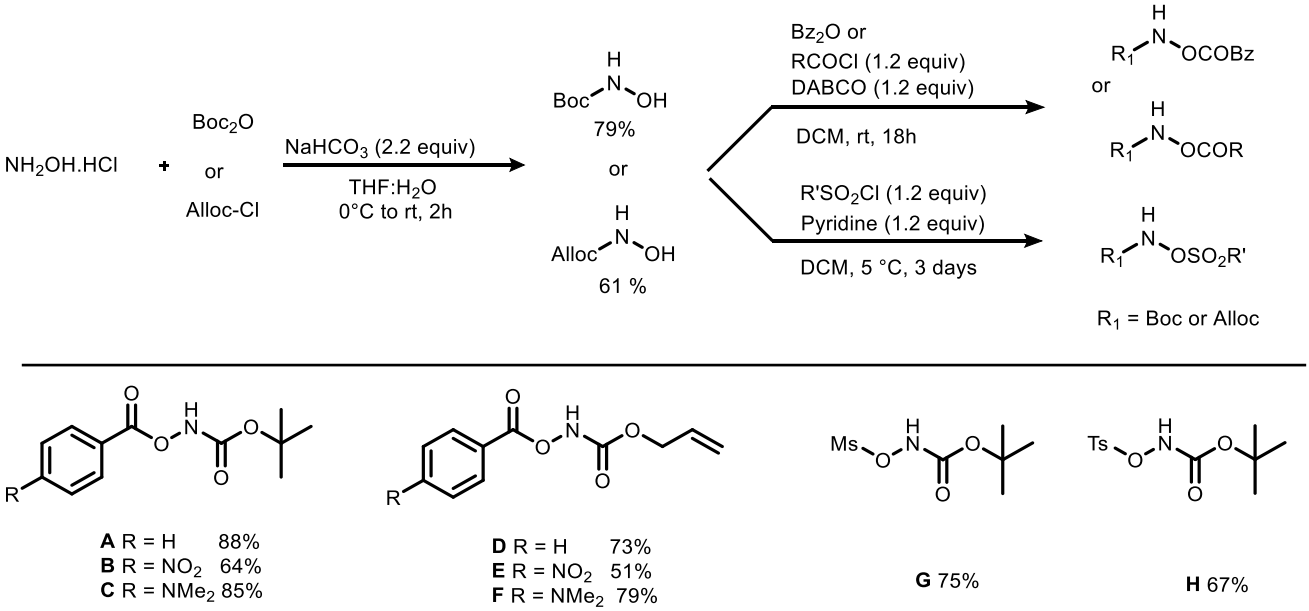


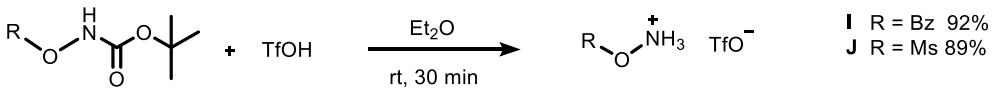
Figure 11 : features of the electrophilic amines.

After a *N*-protection of the hydroxylamine hydrochloride salt with di-*tert*-butyl dicarbonate (Boc_2O) or Allyl chloroformate (Alloc-Cl) groups, the protected product undergoes an *O*-functionalization with benzoyl or sulfonyl group to increase the electrophilicity of the nitrogen atom. Using the following procedures, we synthesized amines **A**-**H** in relative good yields (Scheme 31).[63]



Scheme 31 : synthesized electrophilic amines.

To diversify our serie, we synthesized two other amines salts (**I** and **J**) by removing the Boc group of **A** and **G** compounds in acidic conditions according to known procedure (Scheme 32).[64]



Scheme 32 : synthesis of amine salts.

It is necessary to mention that all the synthesized protected hydroxyl amines are bench stable compounds at room temperature.

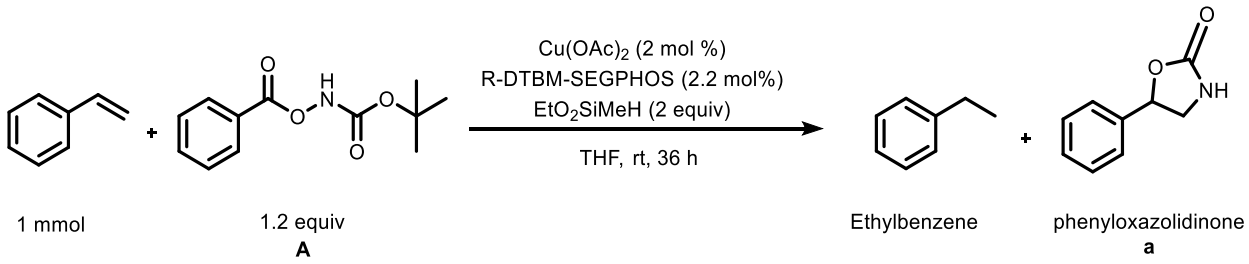
3. Preliminary tests

For our study, styrene was selected as a model substrate for condition discovery, in purpose to apply it later on terpenes. The plan was to use a copper hydride system to catalyze the hydroamination of styrene with the amines already synthesized in the laboratory (**A**-**J**).

Under Buchwald's conditions[62], we examined the freshly prepared amines reactivity with the styrene. As we don't know the stability of most of the amine reagents under heating, we realized the preliminary tests at room temperature (Scheme 33). Started with *tert*-Butylbenzoyloxycarbamate **A** as

[63] J. A. Stafford, S. S. Gonzales, D. G. Barrett, S. M. Suh, P. L. Feldman, *J. Org. Chem*. **1998**, 63, 10040.
[64] L. Legnani, G. P. Cerai, B. Morandi, *ACS Catal*, **2016**, 6, 8162-8165.

simple model of electrophilic amine, we did not obtain the corresponding aminated product. By GC-MS, the measured conversion of styrene is 75 %. The major product was the ethylbenzene resulting from the reduction of the styrene due to the copper hydride system. We were surprised by the presence of traces of phenyloxazolidinone detected GC-MS (Scheme 33).

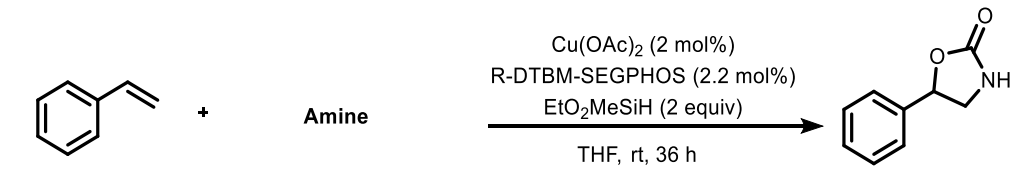


Scheme 33 : preliminary test with styrene.

As well, we did the same test with the allyl benzoyloxycarbamate **D** (Table 1, entry 4) to compare the protecting group's effect. By GC-MS, the measured conversion of styrene was 71 % without any presence for the phenyloxazolidinone or any aminated compound. The only formed product was the ethylbenzene.

We realized this reaction with different tert-Butyl benzoyloxy-carbamate derivatives to see the electronic effect on the benzoyl moiety. The presence of electron withdrawing group like *p*-Nitro **B** (entry 2) does not yield any traces of the cyclic product, while with the amine **C** (entry 3) containing dimethyl amine, an electron donating group in *para* position, traces of oxazolidinone were formed. So, we found a beneficial effect with the electron-rich amine comparing to electron poor one.

Table 1 : oxazolidinone's yields with different tested electrophilic amines.



Entry	Amine	Yield (%)
1	**A**	traces
2	**B**	0
3	**C**	traces
4	**D**	0
5	**E**	0
6	**F**	0
7	**G**	23
8	**H**	12
9	**I**	0
10	**J**	0

The allyl benzoyloxycarbamate derivatives have been tested to check their reactivity in these conditions. **E** and **F** provide ethylbenzene as a single new formed product (Entries 5-6). With the tert-Butyl methanesulfonyloxycarbamate **G**, 23 % of the heterocyclic compound were formed and the analysis of the product by GC-MS revealed the presence of the reduced product in traces amount (Entry 7). We were surprised of the tosyl group effect, as the reaction with **H** (Entry 8) provide just 12 % of the oxazolidinone. Using Amine salts (**I** and **J**), the reaction doesn't provide a noteworthy conversion of the alkene reagent (Entries 9-10).

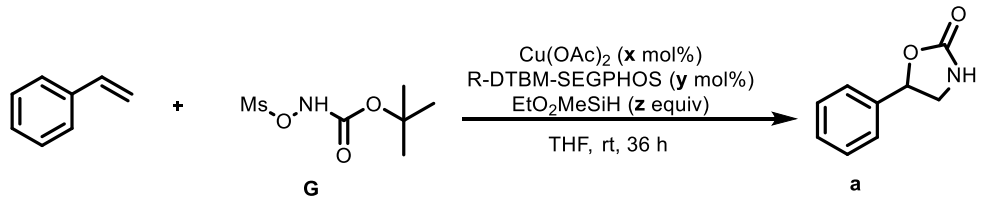
We isolated the heterocyclic compound to prove its structure and we characterize it as 5-phenyloxazolidinone **a**.

Our initial attempts did not afford the desired aminated product, however we obtained an amino-oxygenated compound as by product. Despite the low yield, we were interested in this heterocycle, and curious about this difunctionnalization. So, we decide to study this reactivity and to optimize the conditions.

Providing the highest yield of oxazolidinone and the poorer yield of the reduced product, **G** have been used for the optimization conditions study.

We started by the blank tests to check the effect of some reagents (Table 2). The absence of copper acetate leads to a complete loss of reactivity, without any conversion of styrene (Entry 2). The same result was obtained when we removed the diethoxymethylsilane (Entry 3), showing the importance of this compound. Albeit, the absence of the chiral diphosphine ligand (DTBM-SEGPHOS) is less dramatic but lowering the oxazolidinone yield to 14 % (Entry 4).

Table 2 : blank tests.



Entry	$Cu(OAc)_2$ (mol%)	DEMS (equiv)	SEGPHOS (mol%)	Yield (%)
1	2	2	2.2	23
2	-	2	2.2	0
3	2	-	2.2	0
4	2	2	-	14

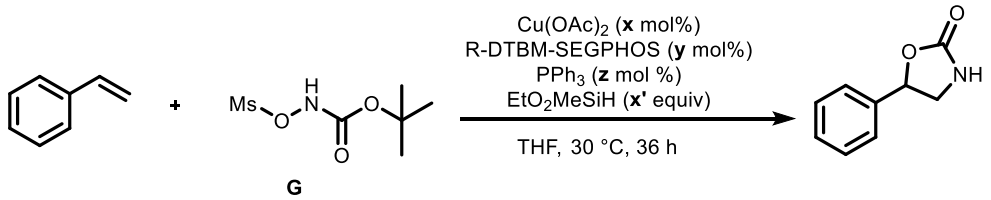
In 2003, Lipshutz has shown that using triphenylphosphine as secondary ligand for the copper hydride catalyzed system applied on asymmetric reduction of aryl ketones, has good effects on the catalyst turnover number.[65] Later Buchwald's group developed the same concept in the alkenes hydroamination to improve the yield.[66] By hypothesis that the DEMS is necessary as hydride source, we applied this strategy and we carried on this reaction in the presence of 4.4 mol% of PPh_3. As expected, the yield has increased to 43 %.

Encouraged by the last result, we focused on the catalytic system to find a solution for the conversion limitation (Table 3). Increasing the catalytic charge in proportional ratio for each constituent, afford an opposite effect and we obtained the oxazolidinone with 35 % (Entry 2). As well, increasing separately to 10 % the quantity of copper acetate, triphenylphosphine and (R)-DTBM-SEGPHOS provide lower yield 40, 31, 37% respectively (Entry 3-5).

[65] B. H. Lipshutz, K. Noson, W. Chrisman, A. Lower, *J. Am. Chem. Soc*. **2003**, 125, 8779.

[66] a) S. Zhu, S. L. Buchwald, *J. Am. Chem. Soc*. **2014**, 136, 15913. b) E. Ascic, S. L. Buchwald, *J. Am. Chem. Soc*. **2015**, 137, 4666.

Table 3 : the effect of the catalytic ratio on the yield.



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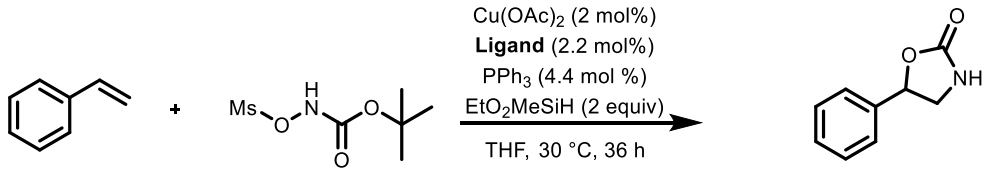
Entry	$Cu(OAc)_2$ (**x** mol%)	SEGPHOS (**y** mol%)	PPh_3 (**z** mol%)	DEMS (**x'** equiv)	Yield (%)
1	2	2.2	4.4	2	43
2	4	4.4	8.8	4	35
3	10	2.2	4.4	2	40
4	2	2.2	10	2	31
5	2	10	4.4	2	37

Meanwhile, by HPLC analysis we deduced that the produced oxazolidinone is racemic. To verify if there is a ligand control, we tested different chiral ligands (Table 4). Under the same conditions, (R)-BINAP showed to be a good ligand candidate for this reaction giving the desired product with a yield of 57% in a racemic manner (Entry 2). (S)-Tol-BINAP and (R)-Xyl-BINAP also produced racemic products, with yields of 51 and 54 % respectively (Entry 3-4). We deduced that the ligand has no effect on the enantioselectivity, subsequently this reaction doesn't necessitate an enantiopure ligand. For that reasons, several ligands have been experienced. Diphosphine ligand such as dppf and dppe appeared to be inactive in the oxazolidinone synthesis with respectively 19 and 5 % of yield (Entry 5-6). Though with 1,2-Bis(diphenylphosphino)benzene revealed no reactivity (0%, Entry 7). Also, amino bidentate ligands like TMEDA and 2,2-Bipyridine were unsuccessful in our reaction conditions (Entry 8-9).

Table 4 : the effect of different ligands on the yield.



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Entry	Ligand	Yield (%)	ee
1	R-DTBM-SEGPHOS	43	racemic
2	R-BINAP	57	racemic
3	S-Tol-BINAP	51	racemic
4	R-Xyl-BINAP	54	racemic
5	dppf	19	-
6	dppe	5	-
7	1,2-Bis(diphenylphosphino)benzene	0	-
8	TMEDA	11	-
9	2,2'-Bipyridine	0	-

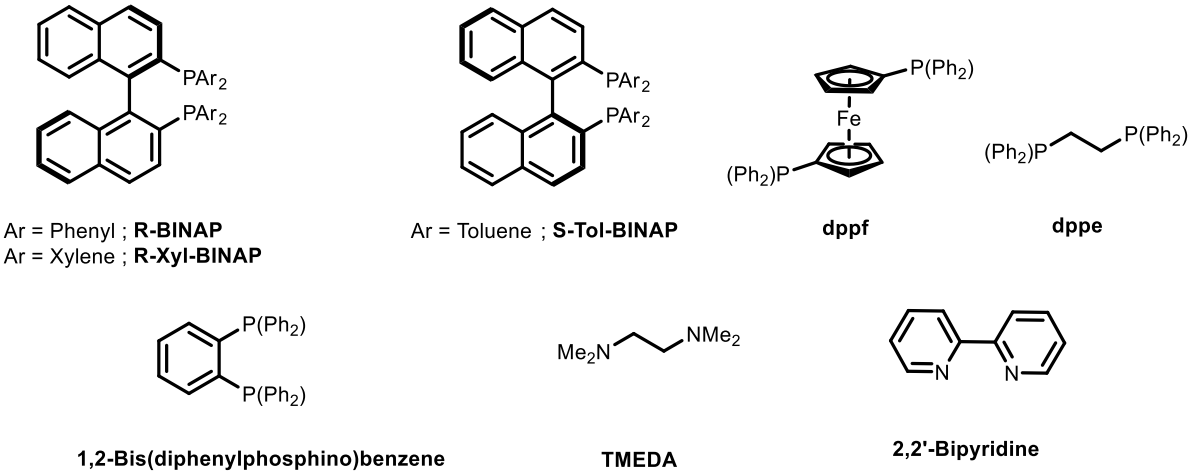
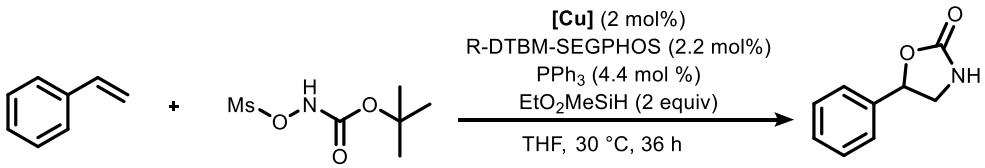


Figure 12 : structures of the tested ligands.

To continue the optimization, we used (R)-BINAP as ligand because it gave the best yield, and because it is cheaper than the racemic one. Both of rac- and (R)-BINAP afforded the same yield.

The following tested parameter was the copper source (Table 5). A serie of copper (II) salts was studied. $Cu(OTf)_2$, $Cu(acac)_2$ and $CuBr_2$ were unsuitable for this reaction and they afforded only traces of product. As the mechanism is unknow, we proposed to check the reactivity of the copper (I). Both of Cu(OAc) and CuI don't yield the desired product. Copper tests did not have a benefit for the yield improvement. Copper (II) acetate showed to have the best catalytic activity (Entry 1).

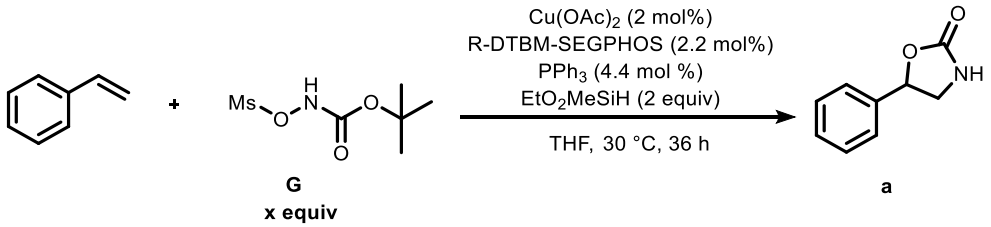
Table 5 : the effect of different ligands on the yield.



Entry	Copper source	Yield (%)
1	$Cu(OAc)_2$	57
2	$Cu(OTf)_2$	3
3	$Cu(acac)_2$	8
4	$CuBr_2$	5
5	Cu(OAc)	0
6	CuI	0

Increasing the electrophilic amine quantity from 1.2 to 2 equiv, raised the yield to 61 % (Table 6, entry 2). On the other hand, repeating this reaction with 3, 4, 5 equiv of amine is relatively nonproductive.

Table 6 : the effect of the amine equivalence on the yield.

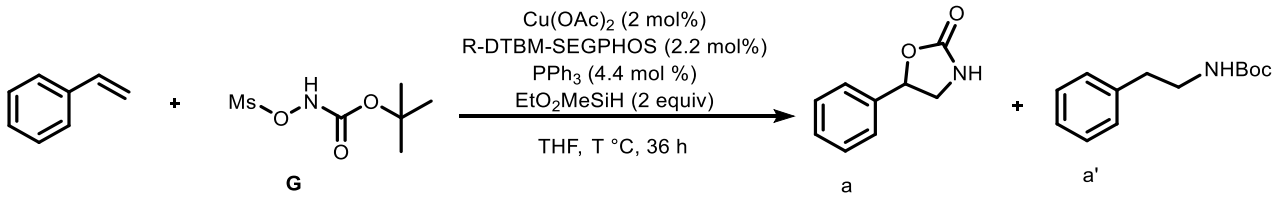


Entry	**G** (x equiv)	Yield (%)
1	1.2	57
2	2	61
3	3	60
4	4	61
5	5	62

These latest results are disturbing because of the non-productive consumption of the amine (excess), which is disappearing in the mixture after the reaction. It might be a reaction between the amine and the copper hydride species providing the decomposition of the first one. What we are not able to explain is the equivalence on hydride comparing to the decomposed amine. In order to avoid this probable decomposition we tried to add the amine in portion wise to the mixture during different hours, but it did not give any success.

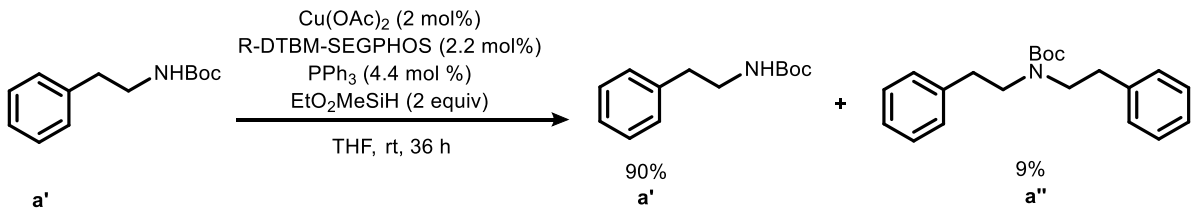
Later, it was found that the result of this reaction is not the same depending on the period of the year, and the room temperature should be more precise (Table 7). When the rt was 15 °C, the oxazolidinone **a** yield decreased to 32 % and we obtained 15% of *tert*-butyl phenethylcarbamate **a'** as by product. It is necessary here to understand the thermal effect. When we set up the reaction at 0°C, there is no reaction and we found the styrene not consumed (Entry 1). While at 30 °C we reproduced the same yield obtained in the best conditions. Increasing more the temperature, the cyclic product yield decreased but with a complete absence of the linear amine. It is maybe due to the instability of the amine at higher temperature.

Table 7 : temperature effect on the reaction.



Entry	Temperature (°C)	Yield of a (%)	Yield of a' (%)
1	0	0	0
2	15	32	15
3	30	61	0
4	>40	8-16	0

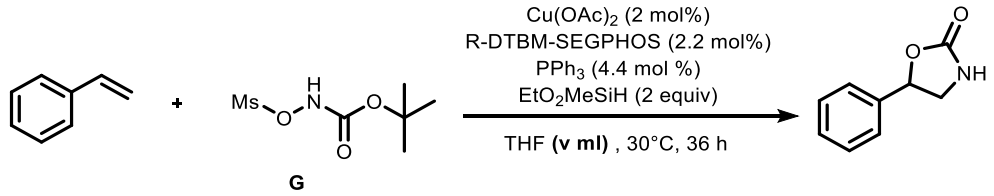
We realized a supplementary test to see if the compound **a'** is the origin of **a**. *Tert*-butyl phenethylcarbamate **a'** was submitted as only reagent under the same catalytic system of our principal reaction to check if it is possible to undergo an intramolecular cyclization providing **a** (Scheme 34). After 36 hours, 90% of **a'** were remaining in the mixture, and 9% of *tert*-butyl diphenethylcarbamate **a''** were formed. So, the protected amine **a'** is probably a byproduct and not an intermediate.



Scheme 34 : behavior of *tert*-butyl phenethylcarbamate in the reaction conditions.

The concentration effect has also been studied (Table 8). Whether with a solvent volume of 2 or 3 ml, the yield is the same (Entries 1-2). Whereas, increasing the concentration to 1 instead of 0.5M cause a complete deactivation of the reaction (Entry 3).

Table 8 : concentration effect on the reaction.



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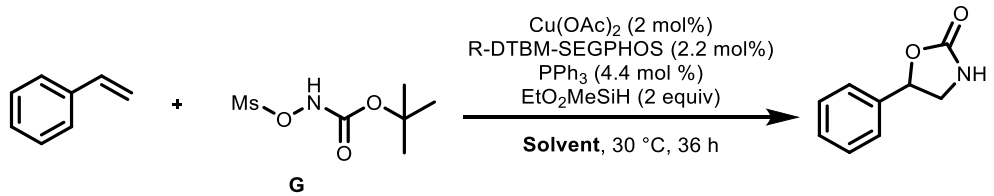
Entry	THF (V ml)	C (M)	Yield%
1	2	0.5	61
2	3	0.33	61
3	1	1	0

Solvents with different properties were used for this reaction (Table 9). Polar aprotic solvents such as DCM, DMF and MeCN gave very low yields, while less polar solvent like 1,4-dioxane afford 71% of desired product with total selectivity. Then, we decided to use 1,4-dioxane as solvent for this reaction.

Table 9 : solvent effect on the reaction.



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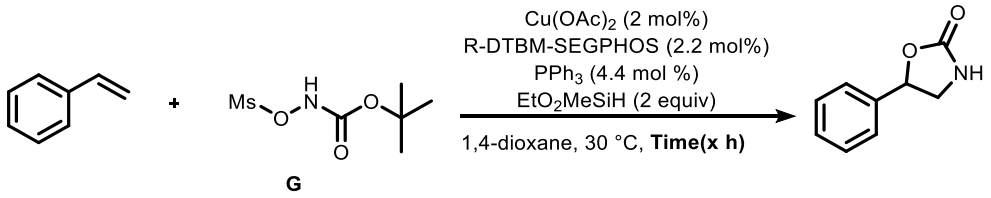
Entry	Solvent	Yield (%)
1	THF	61
2	DCM	10
3	DMF	8
4	MeCN	0
5	1,4-dioxane	71

Kinetic tests have also been realized for this reaction (Table 10). We found that after 16 hours we reached the similar yield obtained at 36 hours. There was no increase of reactivity as the same yield was also obtained when we let the reaction turning for 48 hours.

Table 10 : time effect on the reaction.



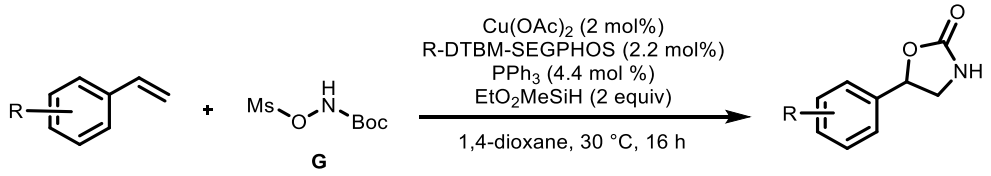
Entry	Time (x h)	Yield (%)
1	36	71
2	16	71
3	48	71

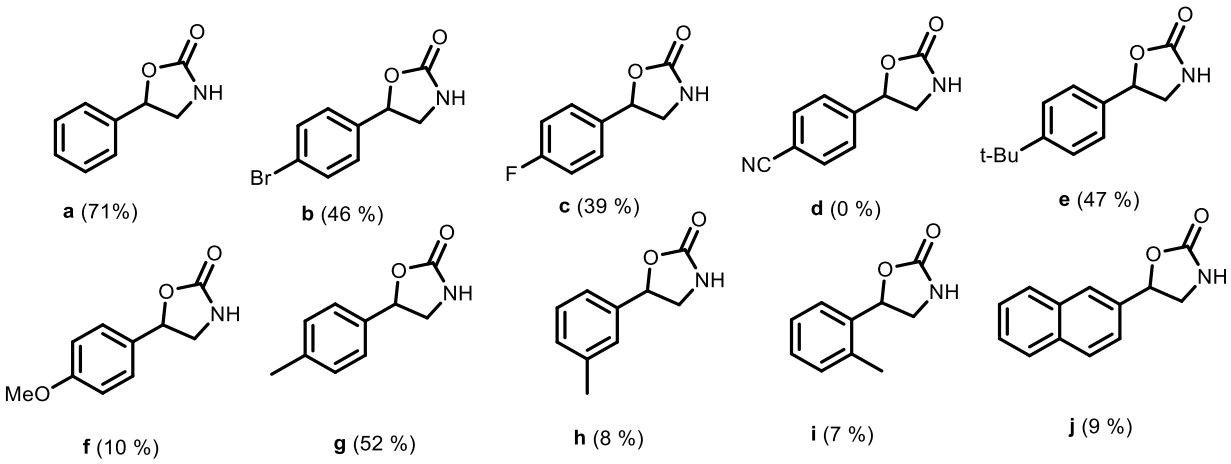
Building on all these tested parameters, we began to apply these conditions on different type of alkene to see the potential of this reaction affording a selective and direct access to oxazolidinone.

4. Scope and limitation

In the first part, we focused our attention on the styrene derivatives to examine electronic and steric effects (Scheme 35).

Styrene bearing a halide like bromide and fluorine on the *para* position afforded the desired product in a moderate yield (46 and 39% respectively for **b** and **c**). The reaction of an alkene with electron withdrawing group like 4-cyanostyrene, did not produce the cyclic product **d**. But the alkene was totally consumed: it might underwent a decomposition under this conditions. Presence of electro donating group on the aromatic moiety has not a homogenous effect on the reactivity. For example, 4-*tert*-butylstyrene provide the corresponding oxazolidinone **e** in 47%, whereas 4-methoxystyrene showed a poor reactivity yielding 10% of product **f**. With 4-methylstyrene, oxazolidinone **g** was obtained with 52 %. Using 3 and 2-methylstyrene, very low yields were obtained (8 and 7% respectively for **h** and **i**). Under the same conditions, 2-vinylnaphtalene afforded only 9% of 5-(naphthalen-2-yl) oxazolidin-2-one **j**.





Scheme 35 : reactivity of styrene derivatives.

Then, we explored the reactivity of 1,1 and 1,2 disubstituted styrene (Figure 13). Cis- and trans-stilbene **k** and **l**, 1,1'-diphenylethylene **m** and trans-beta-methylstyrene **n** are all unsuitable for this reaction. It might be a steric hindrance problem avoiding the alkene difunctionalization.

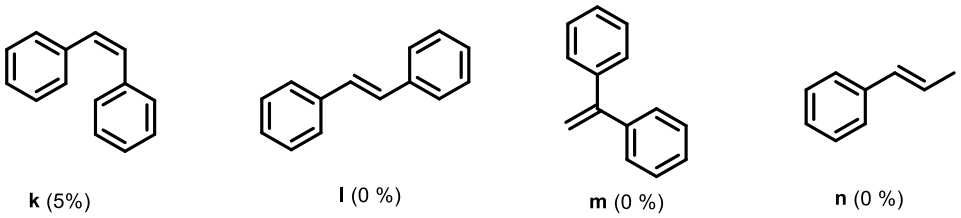


Figure 13 : reactivity of 1,1 and 1,2 disubstituted styrenes.

To expand the scope, we tested various activated and non-activated alkenes (Figure 14). Vinyl ether such as 3,4-dihydro-2H-pyran **o** and (vinyloxy)cyclohexane **p** produced the oxazolidinone with low yield 18 and 12% respectively. While benzofuran afforded 51% of the desired product **q**. Other heterocycle derivatives have been tested and showed high to total unreactivity like indole **r** (15%), benzothiophene **s** and 2-vinylpyridine **t** (0% for both of the cases). As well, indene **u** gave a poor yield of 16%. The same yield was obtained with allylbenzene **v**. Simple aliphatic alkenes presented a very modest reactivity which is the case of cyclohexene **w** (21%) and trans-3-hexene **x** (18%). Dienes as isoprene **y** seems to be unreactive under these conditions and affords just traces of mono reduced product.

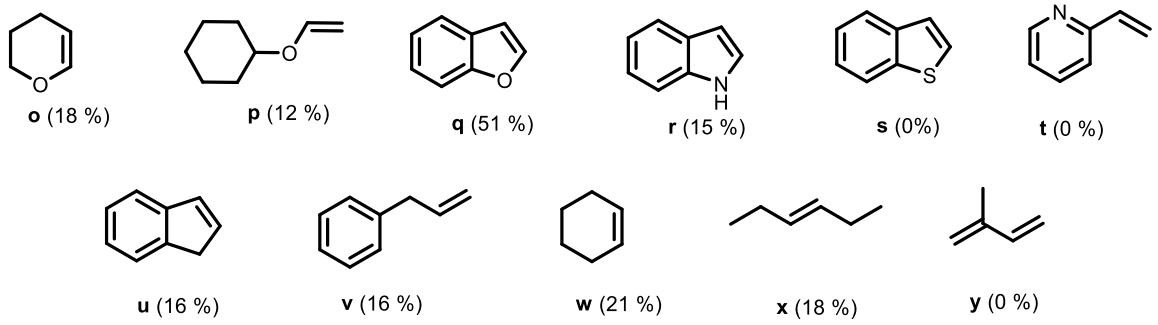


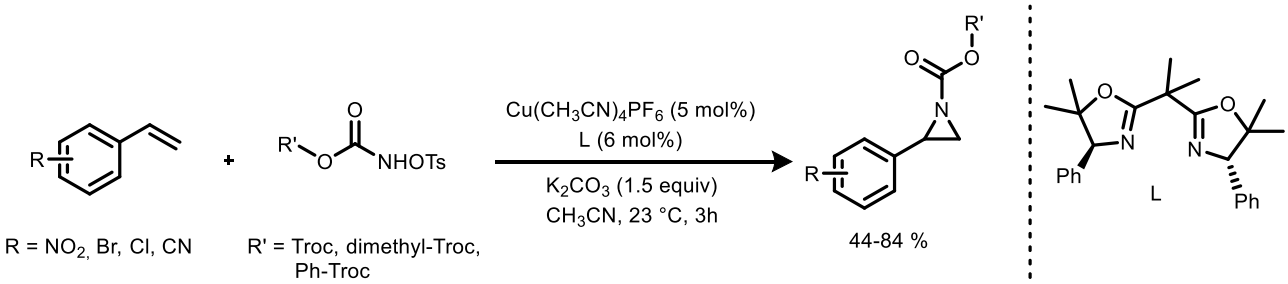
Figure 14 : reactivity of activated and non-activated alkenes.

We were surprised by this lack of reactivity when we change the alkene, so we tried to understand the mechanism to explain the difference of reactivity between the olefins.

Using styrene, we carried out the reaction in the presence of galvinoxyl as a radical scavenger. Any traces of a coupled product with galvinoxyl have been obtained in the end of the reaction, excluding the probability of a radical mechanism.

So, we hypothesized that the reaction starts with the formation of an *N*-Boc-aziridine which will be able to open under some conditions to provide the linear amine (**a'**) or to form a new 5-membered ring cycle (**a**). According to the literature, under thermal condition or in presence of an azaphilic Lewis acid the *N*-Boc-aziridine undergoes a rearrangement to afford the oxazolidinone with elimination of isobutene gas.

The methods already reported to perform the aziridination are principally classed on three types. Aziridine can be formed *via* an intramolecular cyclisation of amidoesters[23], *via* imines[67] or *via* alkenes.[68] Concerning the latter type, many papers described the olefin aziridination, mainly catalyzed by a metal such as copper.[69] For example, Lebel and coworkers described in 2012, styrene derivatives aziridination with tosylcarbamate, by using a copper (I) tetrakis acetonitrile and bis(oxazoline) ligand (Scheme 36).[70] The reaction was carried out in presence of base.



Scheme 36 : aziridation of styrene derivatives

This cyclic product can undergo a ring opening in presence of catalytic amount of Lewis acid and a nucleophile like water or alcohol, to afford the corresponding amino alcohol or ether.

Comparing with the reaction existing in the literature and our reaction conditions, we propose the following mechanism. However, we do not know exactly the role of the DEMS in this reaction. We suppose that the copper is catalyzing the first step and working as Lewis acid in the second step for the initiation of the rearrangement (Scheme 37). It is worthy to note, that we tried to synthesize the *N*-Boc aziridine in order to engage it in the reaction conditions to verify our hypothesis. Unfortunately, we were unable to isolate this three-membered ring: it decomposed during the purification. Marcia de Figueiredo and Greck have already mentioned this problem when they reported an enantioselective synthesis of aziridines.[71] The purification led to a total decomposition when the nitrogen was protected with Boc, Alloc or Cbz group.

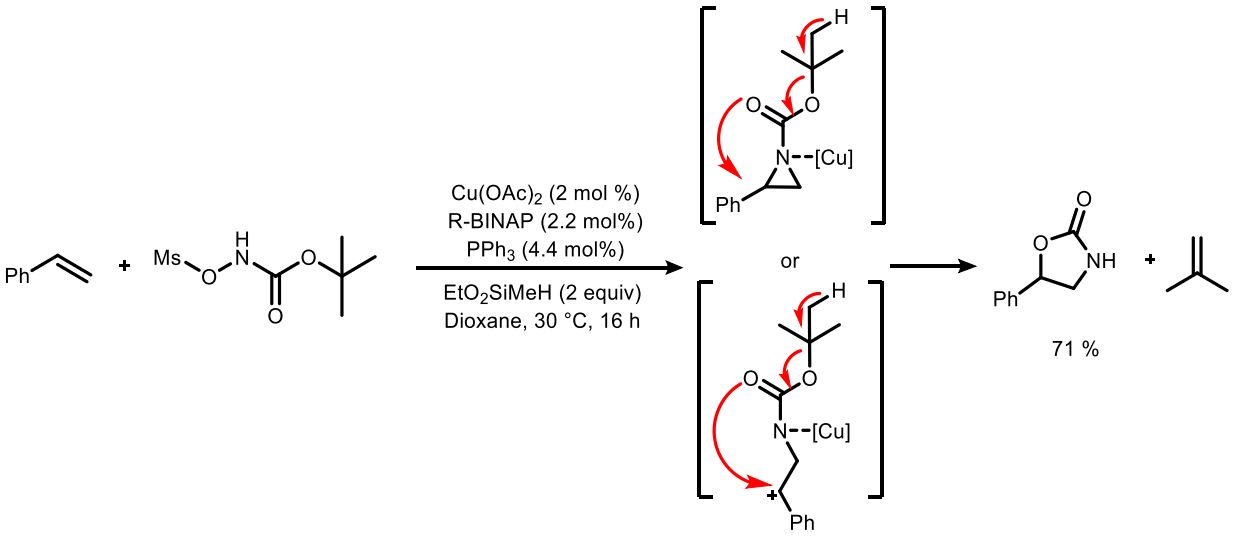
[67] Z. Lu, Y. Zhang, W. D. Wulff, *J. Am. Chem. Soc*. **2007**, 129, 7185.

[68] An example about rhodium catalyzed alkene aziridination : H. Lebel, C. Spitz, O. Leogane, C. Trudel, M. Parmentier, *Org. Lett.*, **2011**, 13, 5461.

[69] D. Tanner, *Angew. Chem. Int. Ed.* **1994**, 33, 599.

[70] H. Lebel, M. Parmentier, O. Leogane, K. Ross, C. Spitz, *Tetrahedron*, **2012**, 68, 3396.

[71] A. Desmarchelier, D. Pereira De Sant'Ana, V. Terrasson, J.-M. Campagne, X. Moreau, C. Greck, R. Marcia De Figueiredo, *Eur. J. Org. Chem.* **2011**, 201, 4046.



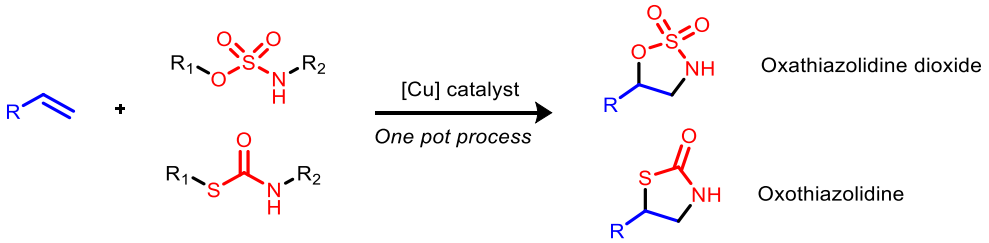
Scheme 37 : proposed mechanism for the oxazolidinone synthesis from styrene.

IV. Conclusion and perspectives

Our initial attempts to develop a simple catalytic system for the hydroamination of alkenes with different amination reagents to afford primary amines failed and produced a completely different and undesirable product. In view of the oxazolidinone moiety importance, we focused on this reaction to improve the reactivity and the yield.

Olefin difunctionalization with amino-oxygenated reagents is an interesting transformation in organic and pharmaceutical synthesis. We reported this kind of transformation to form the regioselective oxazolidinone in one-pot process. Unfortunately, the optimized conditions were not suitable for all the alkene types, which prevented to have a wide scope of difunctionalized alkenes.

Interested by this one pot cyclization, we are looking to synthesize in the laboratory new heterocycles such as oxothiazolidine and oxathiazolidine from alkenes and by using copper catalytic system (Scheme 38). These types of heterocycles have been showed important biological activities. For example, oxothiazolidine presented high anticonvulsant activity.[72]



Scheme 38 : synthesis of oxathiazolidine and oxothoazolidine from alkenes catalyzed by copper.

[72] a) L. L. Sabatier, P. H. Palestro, A. V. Enrique, V. Pastore, M. L. Sbaraglini, P. Martin, L. Gavernet, *J. Enzyme Inhibition Med. Chem.* **2019**, 34, 1465. b) A. E. El-Rakhawy, V. Boshra, A. A. A. Zalata, M.A. Saad, *J. Chem. Pharm. Research*. **2016**, 8, 244.

V. Experimental part

General considerations

All reactions were performed in oven-dried Schlenk flasks under an atmosphere of argon closed with Rodavis® Screw caps. Copper acetate and (R)-BINAP were purchased from Sigma-Aldrich®, used as received, stored in a desiccator cabinet and weighed to air. Diethoxymethylsilane, triphenylphosphine were purchased from Sigma-Aldrich® and used as received. Other reagents were purchased from either Sigma-Aldrich® or Alfa Aesar® or Acros Organics® and used as received.

^{1}H and ^{13}C NMR spectra were recorded with a Bruker AC-400 MHz spectrometer in $CDCl_3$. For ^{1}H NMR (400 MHz), $CHCl_3$ and TMS served as internal standards (δ = 7.26 for $CHCl_3$ and 0 ppm for TMS) and data are reported as follows: chemical shift (in ppm), multiplicity (s = singlet, bs = broad singlet, d = doublet, t = triplet, q = quartet, dd = doublet of doublets, dt = doublet of triplets, td = triplet of doublets, ddd = doublet of doublet of doublets, m = multiplet), coupling constant (in Hz), and integration. For ^{13}C NMR (100 MHz), $CHCl_3$ was used as internal standards (δ = 77.6 ppm) and spectra were obtained with complete proton decoupling. Gas chromatography–mass spectra (GC-MS) were recorded on a Shimadzu QP2012-SE with a Zebron ZB-5MS (20m × 0,18mm), capillary apolar column (Stationary phase: 0.18 µm film). GC-MS method: Initial temperature: 50°C; Initial time: 2 min; Ramp: 22°C/min; Final Temperature: 280°C; Final time: 15min or 23min. HRMS (Q-TOF) were performed on a JEOL JMS-DX300 spectrometer (3 keV, xenon) in a m-nitrobenzyl alcohol matrix. Melting points were measured using Stuart SMP50 Automatic Melting point.

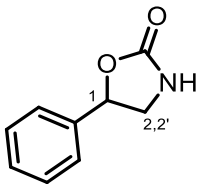
General procedure for the oxazolidinone synthesis

After standard cycles of evacuation and back-filling with argon, an oven-dried Schlenk flask equipped with a magnetic stirring bar was charged with $Cu(OAc)_2$ (3.6 mg, 0.02 mmol, 2.0 mol%), PPh_3 (11 mg, 0. 044 mmol, 4.4 mol%) and (R)-BINAP (23 mg, 0.022 mmol, 2.2 mol%). The tube was evacuated and back-filled with argon. This procedure was repeated three times. Under a stream of argon, distilled 1,4-dioxane (2.0 ml) was added and the mixture was stirred for 10min before the dropwise addition of diethoxymethylsilane (DEMS) (270 mg, 320 µL, 2 mmol, 2.0 equiv). Stirring was continued for an additional 25 min. Then, the alkene (1.0 mmol, 1.0 equiv) and the amine **G** (422 mg, 2 mmol, 2 equiv) were added. The Schlenk was sealed under a positive pressure of argon, stirred at 30 °C for 16 h. Then 1,3,5-trimethoxybenzene (0.33 mmol, 0.33 equiv) was added as internal standard. The reaction mixture was diluted with dichloromethane, then extracted with water for three times. The organic layers were collected and were passed through celite and $MgSO_4$ column. The filter cake being further washed with dichloromethane. The solvent was removed under vacuum. The residue was purified by column chromatography on silica gel.

Experimental procedures and characterization data

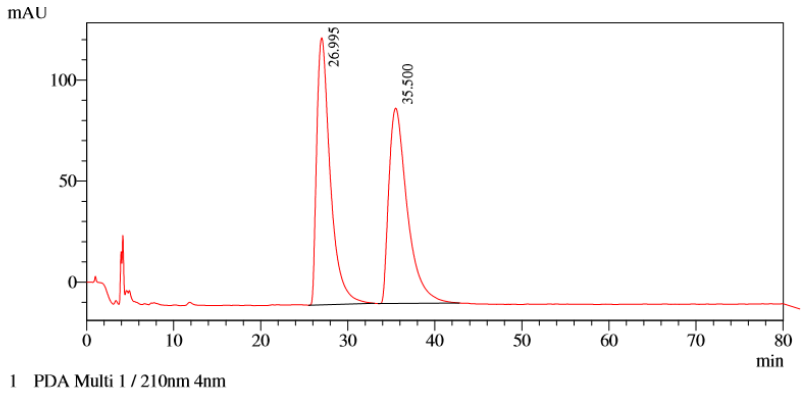
Because of the low yields, we isolated only the oxazolidin-2-one derivatives obtained with a yield up to 30%.

- 5-phenyloxazolidin-2-one **a**[73]:



The reaction of styrene (1mmol, 105 µl) according to the general procedure gave the 5-phenyloxazolidinone **a** in the form of white solid (65 %, 106 mg) after a flash chromatography (pentane :ethyl acetate 90 : 10). The ee was determined by HPLC analysis using a Chiralcel OD-H column (90/10 hexane/i-PrOH; flow rate 0.75 mL/min).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.45 – 7.35 (m, 5H, H_{Ar}), 5.63 (t, *J* = 8.3 Hz, 1H, H_1), 5.54 (bs, 1H, NH), 3.99 (t, *J* = 8.3, 0.7 Hz, 1H, H_2), 3.55 (t, *J* = 8.3, 0.7 Hz, 1H, $H_{2'}$). ^{13}C NMR (101 MHz, $CDCl_3$) δ 160.01, 138.51, 129.12, 129.08, 125.77, 78.02, 48.41. Melting point : 87-92 °C.



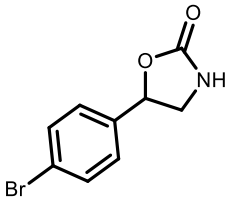
PeakTable

PDA Ch1 210nm 4nm

Peak#	Ret. Time	Area	Height	Area %	Height %
1	26.995	14354960	132110	50.141	57.746
2	35.500	14274340	96668	49.859	42.254
Total		28629300	228777	100.000	100.000

Figure 15 : HPLC analysis. Peak 1 an 2 corresponds respectively to (R) and (S)-5-phenyloxazolidinone[74]

- 5-(4-bromophenyl)oxazolidin-2-one **b** [27]:



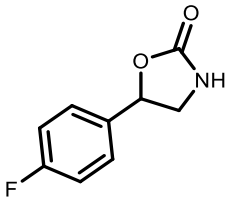
The reaction of 4-bromostyrene (1mmol, 131 µl) according to the general procedure gave the 5-(4-bromophenyl) oxazolidin-2-one **b** in the form of colorless oil (40 %, 96 mg) after flash chromatography (pentane : ethyl acetate 95 : 5 to 80 :20).

[73] Y. Du, Y. Wu, A. Liu, L.-N. He, *J. Org. Chem.* **2008**, 73, 4709.

[74] τ_R is compared to the results existing in the littérature. An example : G. Bartoli, M. Bosco, A. Carlone, M. Locatelli, P. Melchiorre, L. Sambri, *Org. Lett.* **2005**, 710, 1983.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.51 (d, J= 8.31 Hz, 2H), 7.24(d, J= 8.31 Hz, 2H), 5.79(bs, 1H), 5.56(t, J= 8.0 Hz, 1H), 3.80 (t, J= 8.0, 0.71 Hz, 1H), 3.49(t, J= 8.0, 0.71 Hz, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 160.56, 137.55, 131.30, 128.13, 123.31, 76.99, 48.17

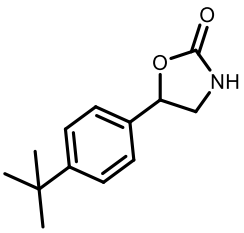
- 5-(4-fluorophenyl)oxazolidin-2-one **c**:



The reaction of 4-fluorostyrene (1mmol, 120 µl) according to the general procedure gave the 5-(4-fluorophenyl) oxazolidin-2-one **c** in the form of brown oil (34 %, 62 mg) after flash chromatography (cyclohexane : ethyl acetate 90 : 10).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.21 (d, J= 8.29 Hz, 2H), 7.18 (d, J= 8.29 Hz, 2H), 5.99 (bs, 1H), 5.31(t, J= 7.9 Hz, 1H), 3.69 (t, J= 7.9, 0.73 Hz, 1H), 3.40(t, J= 7.9, 0.73 Hz, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 160.56, 137.55, 131.30, 129.33, 125.23, 78.17, 49.23

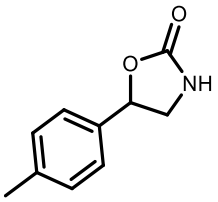
- 5-(4-fluorophenyl)oxazolidin-2-one **e** :



The reaction of 4-*tert*-butylstyrene (1mmol, 138 µl) according to the general procedure gave the 5-(4-*tert*-butylphenyl) oxazolidin-2-one **e** in the form of colorless oil (41 %, 89 mg) after flash chromatography (pentane : ethyl acetate 90 :10).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.47 (d, J= 8.3 Hz, 2H), 7.21 (d, J= 8.3 Hz, 2H), 5.61 (bs, 1H), 5.49 (t, J= 8.1 Hz, 1H), 3.79 (t, J= 8.1, 0.71 Hz, 1H), 3.39 (t, J= 8.1, 0.71 Hz, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 159.50, 137.12, 132.11, 128.13, 124.11, 76.39, 50.12, 34.02, 31.71

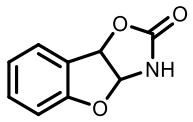
- 5-(*p*-tolyl)oxazolidin-2-one **g** :



The reaction of *p*-tolylstyrene (1mmol, 132 µl) according to the general procedure gave the 5-(*p*-tolyl)oxazolidin-2-one **g** in the form of orange oil (49 %, 87 mg) after flash chromatography (pentane : ethyl acetate 90 :10).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.20 (d, *J* = 7.5 Hz, 2H), 7.15 (d, *J* = 7.5 Hz, 2H), 5.69 (bs, 1H), 5.52 (t, *J* = 8.2 Hz, 1H), 3.88 (t, *J* = 8.2, 0.7 Hz, 1H), 3.47 (t, *J* = 8.2, 0.7 Hz, 1H), 2.30 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 159.93, 138.95, 135.24, 129.78, 126.02, 78.31, 48.24, 20.93.

- 3a,8b-dihydrobenzofuro[2,3-d]oxazol-2(3H)-one **q**:



The reaction of benzofurane (1mmol, 118 μl) according to the general procedure gave the **q** in the form of colorless oil (40 %, 71 mg) after flash chromatography (pentane : ethyl acetate 95 :15 to 80 :10).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.50 (t, *J* = 7.3 Hz, 1H), 7.39 (d, *J* = 7.3Hz, 1H), 7.05 (t, *J* = 7.3 Hz, 1H), 6.93 (d, *J* = 7.3 Hz, 1H), 6.52 (bs, 1H), 6.22 (d, *J* = 6.4 Hz, 1H), 6.12 (d, *J* = 6.4 Hz, 1H).

Chapter II:

Copper catalyzed arylation of ammonia from aryl halides in presence of pyridyldiketone ligands

I. Introduction

Aniline or phenylamine was described for the first time by Otto Unverdorben in 1826. It was isolated from the indigo distillation and called crystallin.[75] The global production of aniline is continuously in progression. Thus, from a total manufacturing of 3.4 million tonnes/year[76] in 2004, it reached 7.5 million tonnes/year in 2018.[77]

Currently, 80% of the aniline production is used for the synthesis of methylene diphenyl diisocyanate which is a monomer used to synthesize polyurethane (MDI, figure 16). MDI results from the condensation of aniline and formaldehyde, followed by the treatment with phosgene to convert the amine to isocyanate function.[77]

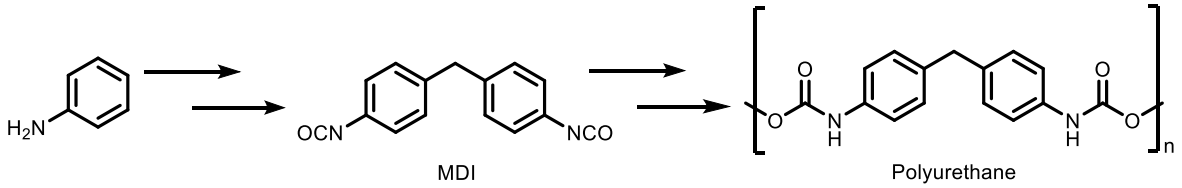


Figure 16 : MDI and its transformation.

Aniline has also been employed for the caoutchouc vulcanization, for herbicide production, for the synthesis of dyes such as mauveine, which is one of the first synthetic dyes.[77]

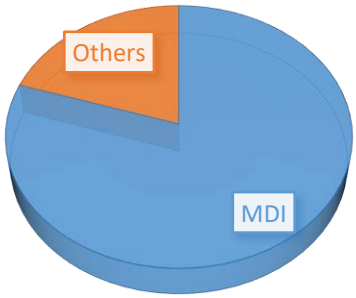


Figure 17 : global use of aniline.

Aniline and its derivatives are key moieties for the synthesis of pharmaceutical products. For example, Mesalazine was approved as medication in 1987 to treat inflammatory bowel disease. Tacrine was the first centrally acting cholinesterase inhibitor used for the treatment of Alzheimer's disease. In addition, aniline derivatives are also used as agrochemical intermediates. For instance, Diuron and Isoproturon are two different herbicides acting as photosynthesis inhibitors. The first one was discovered by Bayer in 1954 (Figure 18).

[75] O. Unverdorben, *Annalen der Physik und Chemie*. **1826**, 8, 397.
[76] H. J. Arpe, *Industrial Organic Chemistry*. Wiley-VCH. 5th edition.
[77] a) According to In-demand Report by Merchant Research & Consulting. http://www.prweb.com/ releases/2014/05/prweb11824259.htm. b) million tonnes/year Global Aniline Market 2015-2019. (2019, october 18). Retrieved from https://www.technavio.com/report/global-aniline-market-2015-2019.

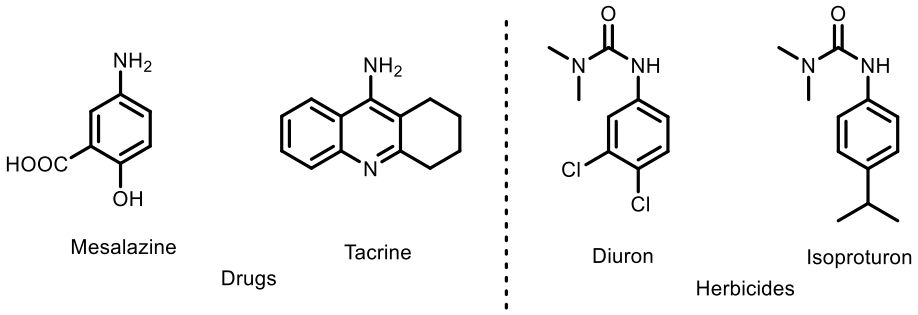
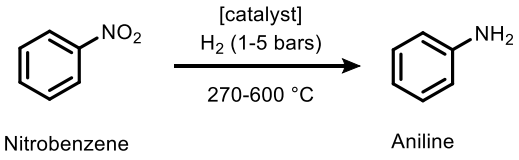


Figure 18 : drugs and herbicides containing aniline moiety.

II. Synthesis of aniline and derivatives: state of the art

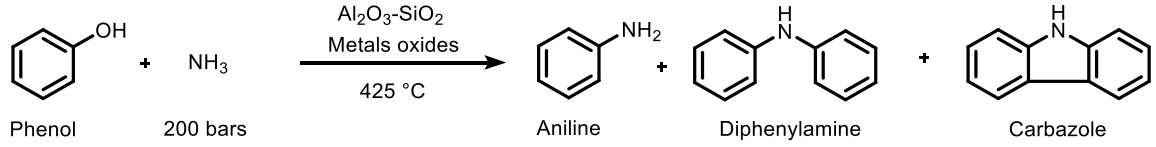
1. Industrial synthesis of aniline

Aniline has been produced in industry for a long time. However, very harsh conditions are still used for the preparation of these compounds. One of the main industrial routes involves nitrobenzene and its hydrogenation under hydrogen pressure (1-5 bars) at high temperature (between 270 and 600°C) in the presence of a catalyst (Scheme 39). The latter could be a metal salt or a mixture of metals such as Ni, Cu, Cr, Fe or Mn. The metallic iron alone can also reduce the nitrobenzene to produce the aniline in harsh conditions.[76]



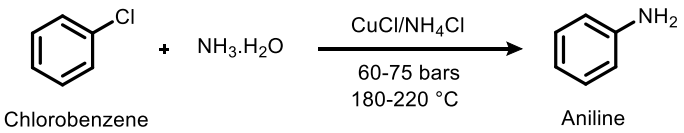
Scheme 39 : synthesis of aniline from the nitrobenzene.

Another industrial route to aniline corresponds to the amination of phenol, realized at 425 °C under 200 bars of ammonia, in the presence of a mixture of metal oxides (TiO_2, B_2O_3) as catalysts and Al_2O_3-SiO_2 (Scheme 40). The aniline is obtained with a selectivity of 87-90% (with 98% of phenol conversion) and the byproducts of this reaction are carbazole and diphenylamine.[76]



Scheme 40 : aniline synthesis from phenol by using Al_2O_3-SiO_2 and metal oxides.

The synthesis of aniline could also be carried out by copper catalyzed amination of chlorobenzene with aqueous ammonia, at temperatures higher than 150°C. A variety of copper salts has been used with different oxidation states (0, I, II). For instance, the process of Kanto Electrochemical company involves the amination of chlorobenzene using aqueous ammonia, a mixture of copper chloride and ammonium chloride at 180-220°C under 60-75 bars to produce aniline and HCl removal (Scheme 41).[76]



Scheme 41 : copper-catalyzed amination of chlorobenzene.

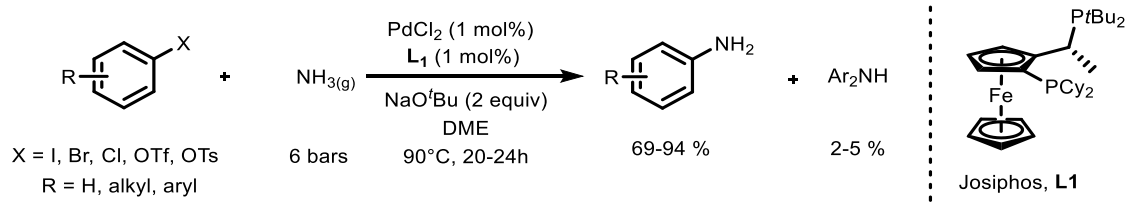
All these methods allow the production of simple aniline in severe conditions (high temperature and/or pressure, strong acidic conditions). Hence, these approaches are hardly compatible with the synthesis of wide range of aniline derivatives.

2. Synthesis of aniline and derivatives

Aniline derivatives and (hetero)anilines are very useful, specially in pharmaceutical industries. However, because they are more sensitive to high pressure and temperature than the unsubstituted aniline, their synthesis requires milder conditions than those described above. Thus, they are usually prepared *via* the coupling of aryl halides and ammonia in the presence catalytic system based on palladium, nickel and copper.

a) Palladium catalyzed amination of aryl halides

In 2006, Hartwig described the coupling of gaseous ammonia (around 6 bars) with aryl iodides, bromides, chlorides and triflates to obtain mono aryl amines in a very good yield and selectivity.[78] This reaction was performed at 90°C with 1 mol% of palladium-Josiphos complex, in presence of sodium *tert*-butoxide (NaO^{t}Bu) as a base (Scheme 42). 10 equiv of lithium amide could also be used for the aryl amination, to replace gaseous ammonia and the additional base. Diaryl amines were also formed as byproducts.



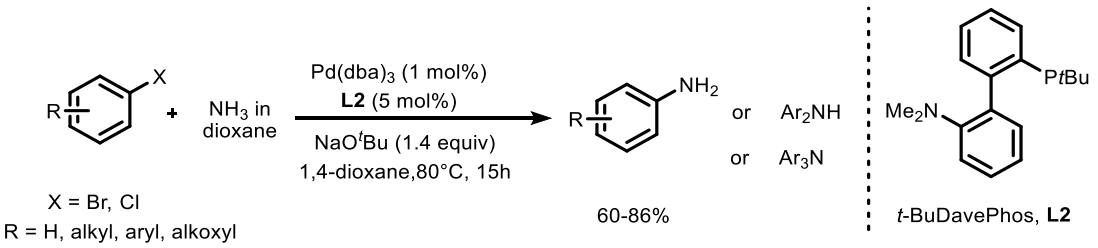
Scheme 42 : palladium-catalyzed arylation of gaseous ammonia.

Later, Hartwig's Group reduced the quantity of gaseous ammonia to 5 equivalents and the catalyst loading to 0.1 mol%, by using an efficient combination of Pd[P(o-tol)$_3$]$_2$ and the sterically hindered alkyl biphosphine ligand Josiphos **L1**. [79]

Using the same catalytic system, they also developed the arylation of different ammonia's surrogates such as ammonium sulfate, ammonium acetate, methylamine and ethylamine hydrochloride salts. This method which requires an excess of base, and it is carried out at 100 °C. These conditions tolerate several aryl chlorides and bromides, especially the *ortho*-substituted ones. The reaction occurs with a high selectivity for the formation of the monoaryl amine over the diaryl amine.[80]

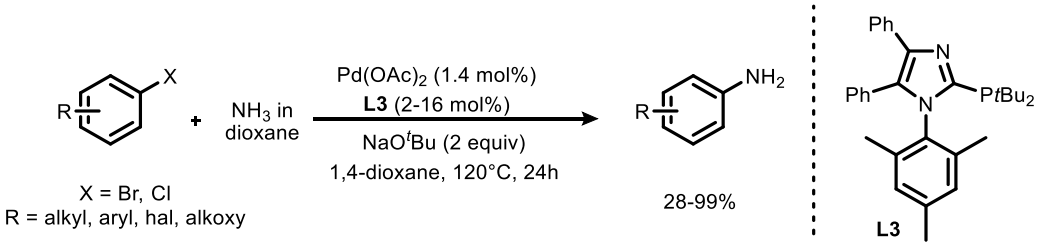
In 2007, the biaryl phosphine ligand (*t*-BuDavePhos) was introduced by Buchwald's group for the coupling of ammonia in dioxane (5 equiv) with aryl halides. By varying the temperature and the concentration of the aryl halide and the ammonia, the reaction could be oriented to the formation of anilines, or to the symmetrical and unsymmetrical di- and triaryl amines (Scheme 43).[81]

[78] Q. Shen, J. F. Hartwig, *J. Am. Chem. Soc.*, **2006**, 128, 10028.
[79] G. D. Vo, J. F. Hartwig, *J. Am. Chem. Soc.*, **2009**, 131, 11049.
[80] R. A. Green, J. F. Hartwig, *Org. Lett.*, **2014**, 16, 4388.
[81] D. S. Surry, S. L. Buchwald, *J. Am. Chem. Soc.*, **2007**, 129, 10354.



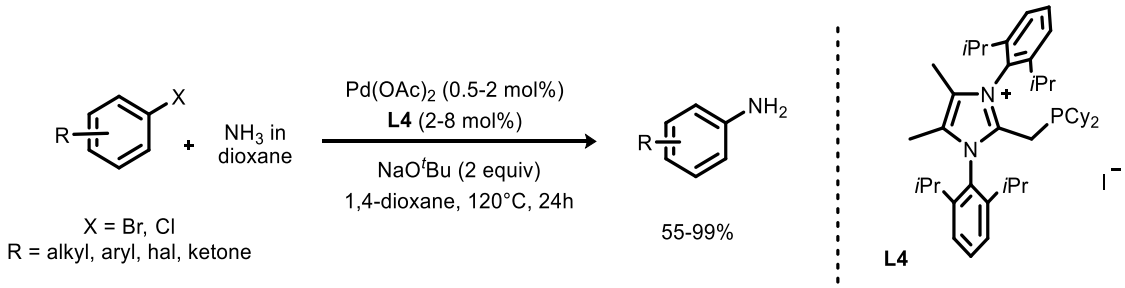
Scheme 43 : palladium-catalyzed amination of aryl chlorides and bromides.

The group of Beller also investigated the arylation of ammonia with palladium catalysis by using a new family of ligands, the dialkyl-2-(N-arylimidazolyl) phosphines **L3**.[82] An ammonia solution in dioxane (5 equiv) has been used at 120 °C to transform the aryl chlorides and bromides into their corresponding anilines with moderate to excellent yields (Scheme 44).



Scheme 44 : palladium-catalyzed amination of aryl bromides and chlorides.

Using imidazolium phosphine **L4** as ligand, Beller's group described a quite similar system which is easily recyclable and reused without any lost of reactivity (Scheme 45).[83]



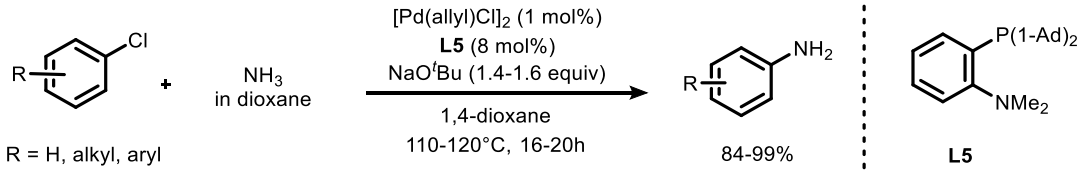
Scheme 45 : palladium-catalyzed amination of aryl halides by using imidazolium phosphane ligands.

In 2010, Stradiotto and coworkers described new ligands for the pallado-catalyzed cross-coupling reaction of aryl chlorides with ammonia.[84] They obtained the corresponding anilines in excellent yields by using 2-(di-1-adamantylphosphino)-*N,N*-dimethylaniline **L5** as ligand. The reactions were performed in dioxane at 110 to 120 °C in the presence of a strong base NaO^{t}Bu(Scheme 46).

[82] T. Schulz, C. Torborg, S. Enthaler, B. Schffner, A. Dumrath, A. Spannenberg, H. Neumann, A. Bçrner, M. Beller, *Chem. Eur. J*. **2009,** 15, 4528.

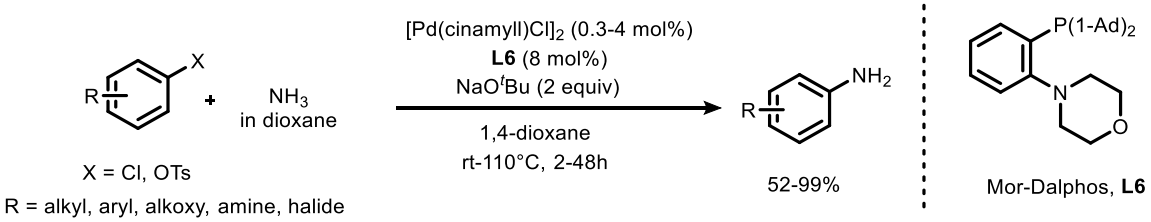
[83] a) A. Dumrath, X.-F. Wu, H. Neumann, A. Spannenberg, R.Jackstell, M. Beller, *Angew. Chem. Int. Ed*. **2010**, 49, 8988. b) A. Dumrath, C. Lubbe, H. Neumann, R. Jackstell, M. Beller, *Chem. Eur. J.* **2011**, 17, 9599.

[84] R. J. Lundgren, A. Sappong-Kumankumah, M. Stradiotto, *Chem. Eur. J.* **2010**, 16, 1983.



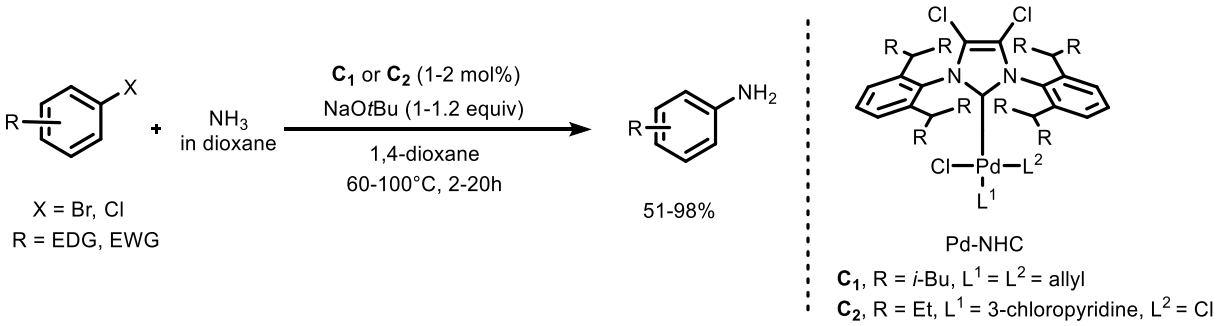
Scheme 46 : palladium-catalyzed arylation of NH_3 with aryl chlorides.

Thereafter, the same group explored a more efficient ligand (Mor-Dalphos **L6**) able to promote with high yield and excellent selectivity the amination of a variety of aryl chlorides at 50-110 °C, and aryl tosylates as well at room temperature.[85] This ligand, similar to **L5**, bears a morpholine group instead of the two-methyl substituents (Scheme 47).



Scheme 47 : palladium-catalyzed amination of aryl chlorides and tosylates.

Organ was the first to present a pallado-catalyzed monoarylation of ammonia performed with a ligand of non-phosphine type. In 2017, his group introduced the *N*-heterocyclic carbene as phosphine alternative to prepare with high yields aniline derivatives from aryl bromides and chlorides.[86] This reaction was carried out with NaO^{t}Bu in dioxane at 60 to 100 °C (Scheme 48).



Scheme 48 : Organ's method for the amination of aryl chlorides and bromides.

b) Nickel catalyzed amination of aryl halides

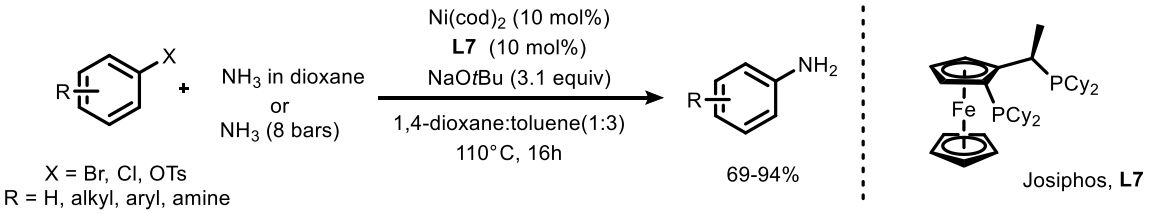
Nickel complexes have been used to catalyze the coupling of aryl chlorides with primary and secondary amines.[87] Inspired by these methods, different groups studied the possibility to carry out the synthesis of anilines derivatives from aryl chlorides.

[85] R. J. Lundgren, B. D. Peters, P. G. Alsabeh, M. Stradiotto, *Angew. Chem. Int. Ed.* **2010**,49, 4071.

[86] C. Lombardi, J. Day, N. Chandrasoma ,D. Mitchell, M.J. Rodriguez, J. L. Farmer, M. G. Organ, *Organometallics*. **2017**, 36, 251.

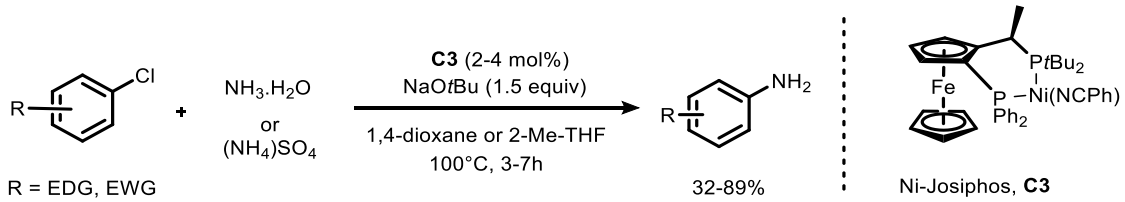
[87] Some examples: a) J. P. Wolfe, S. L. Buchwald. *J. Am. Chem. Soc.* **1997**, 119, 6054; b) C.-Y. Gao, L.-M. Yang. *J. Org. Chem*. **2008**, 73, 1624; c) F. Nathel, J. Kim, L. Hie, X. Jiang, N. K. Garg. *ACS Catal*. **2014**, 4, 3289; d) N. H. Park, G. Teverovskiy, S. L. Buchwald. *Org. Lett*. **2014**, 16, 220.

In 2015, Stradiotto's group demonstrated that the association of $Ni(cod)_2$ and Josiphos ligand **L7** allows the formation of aniline derivatives from aryl chlorides, bromides and tosylates at 110 °C in presence of NaO^tBu as base (Scheme 49). [88]



Scheme 49 : nickel-catalyzed synthesis of aniline from aryl chlorides.

In the same period, Hartwig and coworkers employed a complex of nickel (0)/Josiphos to reach the same goal. [89] In this complex, the nickel (0) is stabilized by the benzonitrile. The advantageous of their system is the kinetic of the reaction: they were able to obtain the anilines from ammonium solution or ammonium sulfate in good to excellent yield in 3 to 7 hours at 100°C (Scheme 50).

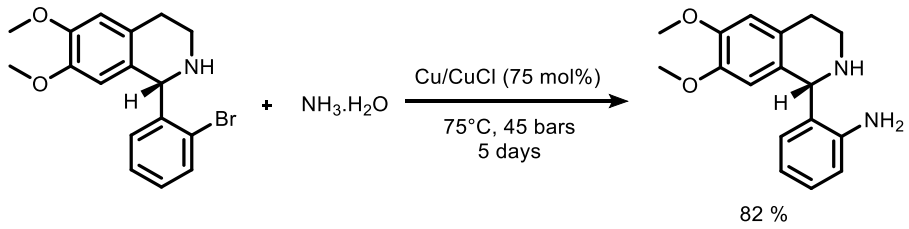


Scheme 50 : nickel-catalyzed arylation of ammonia and ammonium sulfate from aryl chlorides.

c) Copper-catalyzed amination of aryls halides

Related to its abundance, cheapness and low toxicity, copper proved to be a good alternative to the use of palladium and nickel catalysts for the arylation of ammonia.

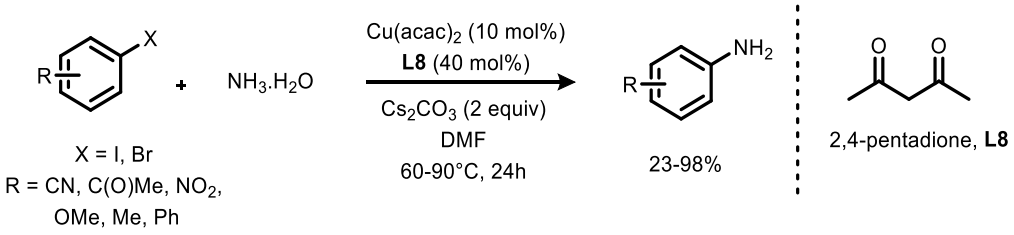
In 1999, Suna's group described the synthesis of the (S)-1-(2-aminophenyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinolineamination by amination of the corresponding aryl bromide with an ammonia solution (as both solvent and reagent). By using almost stoichiometric amounts of Cu/CuCl (75 mol% of copper) the desired product was obtained with 82 % of yield. The reaction carried out at 75 °C under 45 bars for 5 days, was not extended to other examples (Scheme 51).[90]



Scheme 51 : amination of (S)-1-(2-bromophenyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinolineamination by using copper system.

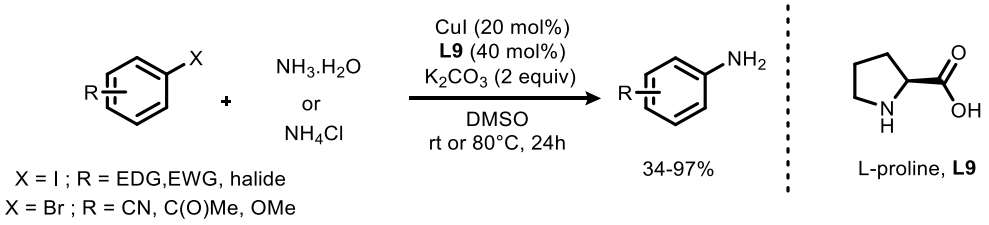
[88] A. Borzenko, N. L. Rotta-Loria, P. M. MacQueen, C. M. Lavoie, R. McDonald, M. Stradiotto. *Angew. Chem., Int. Ed*. **2015**, 54, 3773.
[89] R. A. Green, J. F. Hartwig, *Angew. Chem., Int. Ed.* **2015**, 54, 3768.
[90] E. Vedejs, P. Trapencieris, E. Suna, *J. Org. Chem.*, **1999**, *64*, 6724.

In 2007, our group discovered a new catalytic system allowing the arylation of aqueous ammonia from aryl iodides and aryl bromides as well.[91] The system is based on copper acetylacetonate (II) used as precatalyst and associated to acetylacetone (acac) **L8**, which is a very simple and cheap ligand. The reaction was successfully performed at 60-90°C in DMF in presence of 2 equivalents of cesium carbonate, from aryl halides bearing electron withdrawing and electron donating EWG and EDG substituents in various position (*o*, *m* and *p*) (Scheme 52).



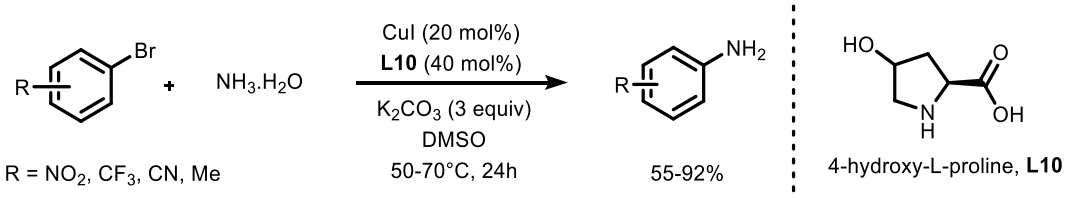
Scheme 52 : copper-catalytic system for ammonia arylation with 2,4-pentadione ligand.

In 2008, Chang's group developed the arylation of aqueous ammonia as well as ammonium chloride by using copper iodide (I) associated to L-proline **L9** ligand, in presence of K_2CO_3 in DMSO.[92] This system allows the formation of aniline derivatives at room temperature from aryl iodides (scheme 53). This catalytic system was also successfully tested at 80 °C with three couples of aryl bromide.



Scheme 53 : copper-catalyzed arylation of ammonia or ammonium chlorides with L-proline.

In 2009, Ma's group described aryl bromides amination by using copper iodide and 4-hydroxy-L-proline **L10** as ligand at 50 °C.[93] This system, quite similar to the one presented by Chang, tolerates various electron withdrawing and electron donating groups on the aromatic cycles (Scheme 54). Recently, the same group reported another system using Cu_2O associated to *N*-(naphthalen-1yl)-*N*'-alkyl oxalamide ligands. This combination allowed to work with low loading of catalyst and ligand.[94]



Scheme 54 : Ma's method for the amination of aryl bromides with 4-hydroxy-L-proline ligand.

Since these advances, many groups focused on the direct copper catalyzed arylation of ammonia (Scheme 55).

---

[91] a) Procédé de Synthèse d'arylamines, M. Taillefer, N. Xia, Fr **2007** 06827 and PCT **2008** 051701; b) N. Xia, M. Taillefer, *Angew. Chem., Int. Ed*. **2009**, 48, 337–339.

[92] J. Kim, S. Chang. *Chem. Commun*. **2008**, 3052.

[93] L. Jiang, X. Lu, H. Zhang, Y. Jiang, D. Ma. *J. Org. Chem*. **2009**, 74, 4542.

[94] J. Gao, S. Bhunia, K. Wang, L. Gan, S. Xia, D. Ma. *Org. Lett.* **2017**, 19, 2809.

Ding's group introduced the use of 1-(5,6,7,8-tetrahy-droquinolin-8-yl)-2-methylpropan-1-one **L11** (10 mol%) as ligand with copper bromide (5 mol%) to perform the amination of aryl iodides at room temperature. Higher temperature (110 °C) and higher catalyst loading (20 mol% of ligand and 10 mol% of copper) are needed to achieve the arylation of aryl bromides.[95]

Wolf's group described the arylation of aqueous ammonia in mixture of water and *N*-methyl pyrrolidinone (NMP) (1:1) by using copper (I) oxide at 80°C in the case of aryl iodides and bromides. [96] The same conditions were used at 110°C under microwave irradiation to perform the amination of aryls chlorides but the results were difficult to reproduce.[97]

In 2010 Wan's group, developed the amination of aryl iodides and bromides in water with the presence of tetrabutylammonium bromide (TBAB) at 120°C, by using copper oxide (II) associated to N^2,N^2-diisopropyloxalohydrazide **L12**.[98]

Later Jiang and his coworkers introduced the use of 2-carboxylic acid-quinoline-*N*-oxide **L13** with copper iodide to promote the amination of aryl iodides at 50 °C.[99]

Using copper iodides as well, Sekar's introduced the use of D-glucosamine hydrochloride **L14** as ligand to achieve the amination of aryl iodides and bromides at 110°C, in a mixture of acetone and water.[100]

In 2012, the amination of aryl iodides and bromides was described by Wan's group by using a recyclable catalytic system composed of copper sulfate and sucrose **L15**. This reaction was carried out at 90 °C in water and polyethylene glycol.[101]

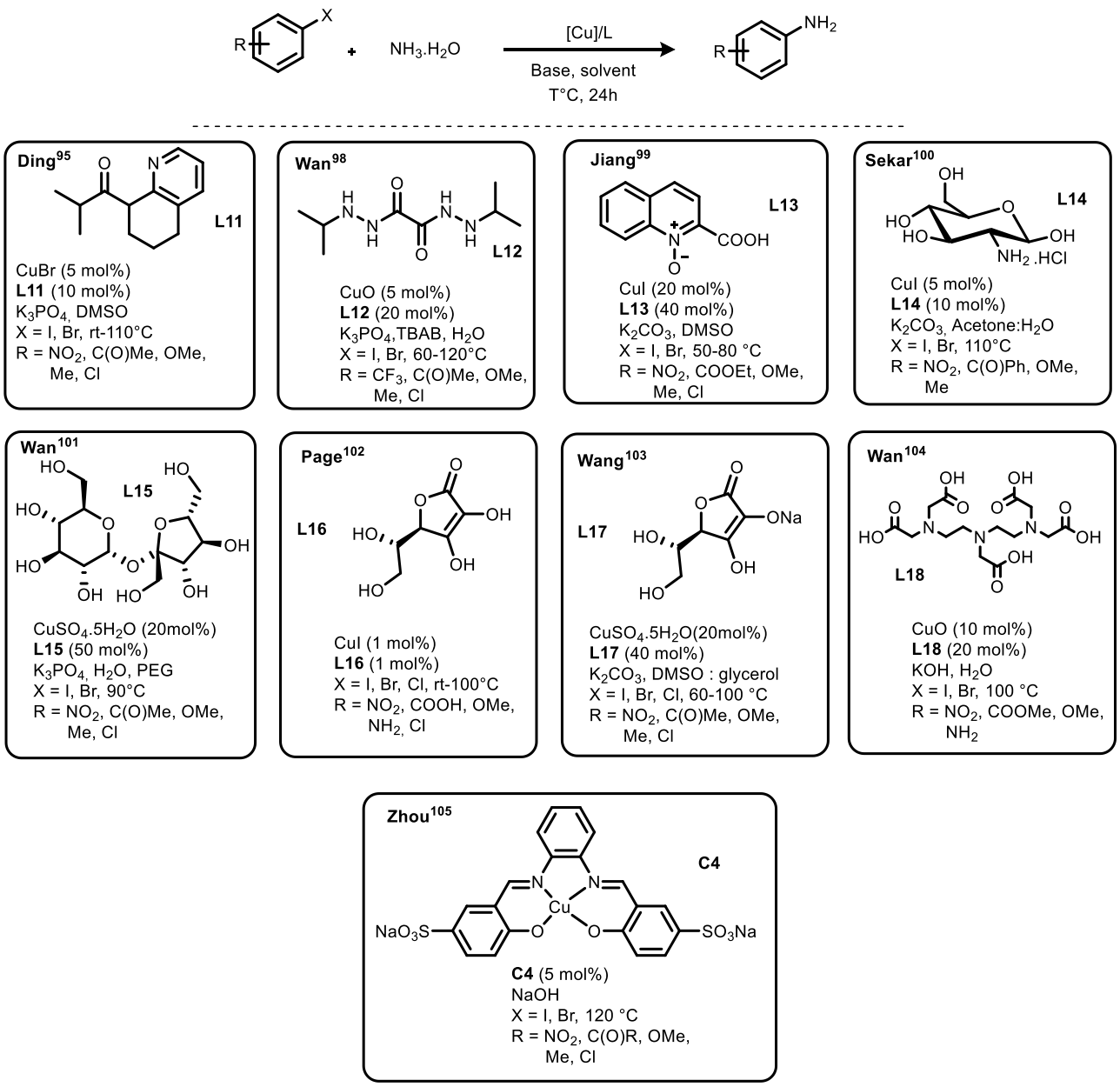
In the same year, the group of Page demonstrated that 1 mol% of copper iodide and 1 mol % of ascorbic acid **L16** could promote the amination of aryl iodides, bromides and electron poor aryl chlorides in very good yields. In the case of aryl bromides and chlorides, a higher temperature is required (100 °C).[102]

Later, Wang's group associated the copper sulfate to sodium ascorbate **L17** to perform the arylation of ammonia in a mixture of DMSO and glycerol at 60-100 °C.[103] This reaction was applied on aryl iodides, bromides and chlorides. It is worthy to note that the aryl chloride aminations reported by Page's and Wang's groups were restricted to the aromatic cycles bearing EWG substituents and in particulary to the nitro groups for which a nucleophilic aromatic substitution is possible.

In 2014, Wan and his coworkers developed a new catalytic system for the amination reaction by using copper (II) oxide with diethylene triaminepentaacetic acid **L18** as ligand. This method was performed with aryl bromides and iodides in water at 100 °C.[104]

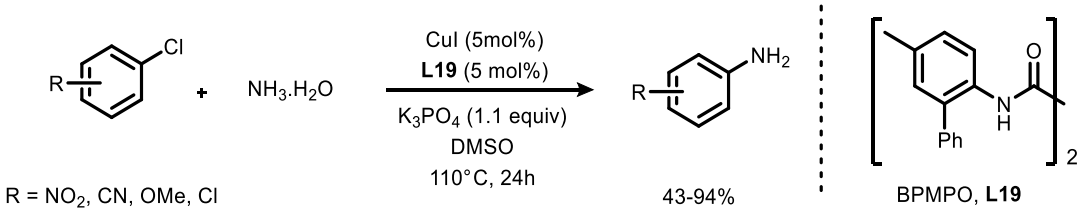
Finally, in order to develop the aqueous catalysis, Zhou's group synthesized sulfonate-Cu(salen) **C4** as copper complex to achieve the amination of aryl iodides and aryl bromides at 120 °C.[105]

[95] D. Wang, Q. Cai, K. Ding. *Adv. Synth. Catal.* **2009**, 351, 1722.
[96] H. Xu, C. Wolf. *Chem. Commun.* **2009**, 3035.
[97] G. D. Vo, J. F. Hartwig, *J. Am. Chem. Soc.* **2009**, 131, 11049.
[98] F. Meng, X. Zhu, Y. Li, J. Xie, B. Wang, J. Yao, Y. Wan. *Eur. J. Org. Chem.* **2010**, 2010, 6149.
[99] X. Zeng, W. Huang, Y. Qiu, S. Jiang. *Org. Biomol. Chem*. **2011**, 9, 8224.
[100] K. G. Thakur, D. Ganapathy, G. Sekar, *Chem. Commun*. **2011**, 47, 5076.
[101] M. Huang, L. Wang, X. Zhu, Z. Mao, D. Kuang, Y. Wan, *Eur. J. Org*. *Chem*. **2012**, 4897.
[102] P. Ji, J. H. Atherton, M. I. Page, *J. Org. Chem.* **2012**, 77, 7471.
[103] Z. Quan, H. Xia, Z. Zhang, Y. Da, X. Wang. *Chin. J. Chem*. **2013**, 31, 501.
[104] B. Yang, L. Liao, Y. Zeng, X. Zhu, Y. Wan. *Catal. Commun*. **2014**, 45, 100.
[105] Z. Wu, Z. Jiang, D. Wu, H. Xiang, X. Zhou. *Eur. J. Org. Chem.* **2010**, 1854.



Scheme 55 : different ligands inolved in aryl halides amination.

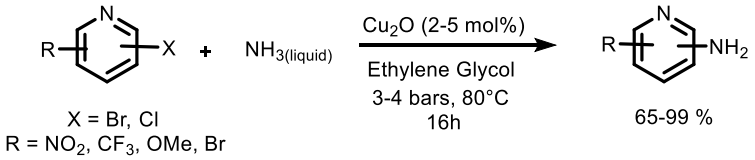
In 2015, Ma's group employed copper (I) iodide and *N,N'*-bis(2-phenyl-4-methylphen-yl)-oxalamide BMPO **L19** for the amination of challenging aryl chlorides substituted by EWG and EDG.[106] This method allows the formation of aniline derivatives in very good yields (Scheme 56).



Scheme 56 : copper-catalyzed amination of aryl chlorides with BMPO ligand.

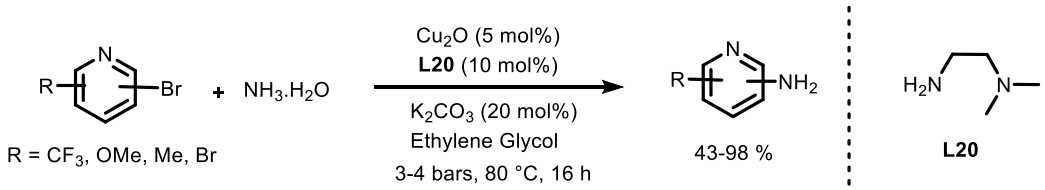
[106] M. Fan, W. Zhou, Y. Jiang, D. Ma. *Org. Lett*. **2015**, 17, 5934.

In some of the methods cited above, the authors reported few examples for the amination of heteroaryl halides. However, some groups have developed the heteroaryl amination widely. In 2001, Merck research laboratories reported the arylation of liquid ammonia catalyzed by 2-5 mol% of copper oxide in ethylene glycol at 80°C in a reactor under pressure (3-4 bars). The application of this method is limited to *N*-heterocycle halides, activated aryl bromides and iodobenzene (Scheme 57).[107] This reaction presents several other drawbacks such as the use of liquid ammonia and the arylation of ethylene glycol observed with some substrate.



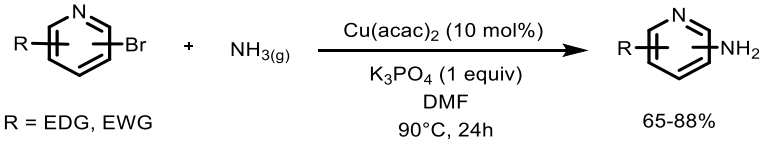
Scheme 57 : copper-catalyzed amination of *N*-heterocycle halides.

Fischmeister, Thomas and Renaud synthesized several dipyridylamine ligands based on the method presented above.[108] They also developed an improved system by working with aqueous ammonia instead of the liquid ammonia. They employed copper (I) oxide associated to *N*,*N*-dimethyl ethylenediamine **L20** in ethylene glycol to realize the amination of the bromopyridine and of pyrimidine derivatives. The reaction is carried out at 60 °C and tolerates various substituents on the aromatic ring (Scheme 58).[109]



Scheme 58 : copper-catalyzed amination of bromopyridine and pyrimidine.

Later, Fantasia's group described the amination of heteroaryl bromides with gaseous ammonia at 90°C by using $Cu(acac)_2$ with potassium phosphate in DMF. The authors supposed that the counter anion of the copper(acetylacetonate) acts as a ligand (Scheme 59).[110]



Scheme 59 : copper-catalyzed amination of bromopyridine derivatives.

3. Conclusion

Since it has been discovered, the transition metal-catalyzed direct amination of aryl halides with NH_3 has become one of the most applied way to produce aniline derivatives.[111] However, the corresponding methods present some limitations and drawbacks (Table 11). For example, beside the high cost and the low abundance, palladium-catalyzed systems often require expensive ligands,

[107] F. Lang, D. Zewge, I. N. Houpis, R. P. Volante, *Tetrahedron Lett.* **2001**, 42, 3251.
[108] S. Gaillard, M. K. Elmkaddem, C. Fischmeister, C. M. Thomas, J-L. Renaud. *Tetrahedron. Lett.* **2008**, 49, 3471.
[109] M. K. Elmkaddem, C. Fischmeister, C. M. Thomas, J-L. Renaud. *Chem.Commun*., **2010**,46, 925.
[110] S. Fantasia, J. Windisch, M. Scalone. *Adv. Synth. Catal*. **2013**, 355, 627.
[111] J. Schranck, A. Tlili. *ACS Cat*., **2018**, 8, 405.

ammonia surrogates and in some cases high temperatures. Nickel is cheaper than palladium but the main disadvantages are the high toxicity and the air sensitivity of the catalysts (such as nickel 0) together with the costly ligands used for the ammonia arylation.

Table 11 : general features for the systems allowing the transition metal-catalyzed direct arylation of NH_3.

	[Pd]	[Ni]	[Cu]
Temperature	moderate to high	high	moderate to high
Pressure	moderate to high	atmospheric	atmospheric
Cost	expensive	inexpensive	inexpensive
Toxicity	high	high	low
Stability	high	low	high

Copper as cheaper, more abundant and low toxic metal (comparing to both palladium and nickel) has proved to be an excellent catalyst for this type of coupling. It is worthy to note that comparing to palladium and nickel catalytic systems, the ligands engaged in the copper-catalyzed arylation of NH_3 are usually simple, cheap and less toxic. One of the last objective in this field consists in achieving the amination of aryl chlorides or to proceed the amination of aryl iodides and bromides at room temperature.

In this context, we report the use of simple and easy handle pyridyl diketone ligands type to undergo the copper-catalyzed arylation of ammonia from aryl iodides and bromides under mild temperature conditions.

This work was realized through a collaboration with the team of Prof. Artur R. Stefankiewicz from the Adam Mickiewicz University in Poznan.

III. New copper catalytic systems for the arylation of NH_3

1. Presentation of the used ligands

Pyridyldiketones contain, after deprotonation, two distinct coordination sites of different nature: an anionic β-diketonate and a neutral pyridine (Figure 19).

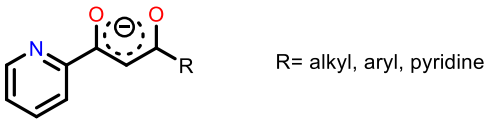


Figure 19 : the potentiel binding sites of pyridyl diketone ligands.

These types of compounds have been used as ambident ligands in various fields such as supramolecular chemistry to form metallacycles and cages.[112] Likewise, they were used in coordination chemistry to prepare various complexes with metals such as copper[113], cobalt[113], palladium[114] and iron[115], and for the preparation of bimetallic complexes involving manganese and silver atoms.[116]

[112] a) G.L. Wang, Y. J. Lin, H. Berke, G. X. Jin, *Inorg. Chem.,* **2010**, 49, 2193. b) M. Wang, V. Vajpayee, S. Shanmugaraju, Y. R. Zheng, Z. Zhao, H. Kim, P. S. Mukherjee, K. W. Chi, P. J. Stang, *Inorg. Chem.,* **2011**, 50, 1506. c) H. B. Wu, Q. M. Wang, *Angew. Chem. Int. Ed.* **2009**, 48, 7343.

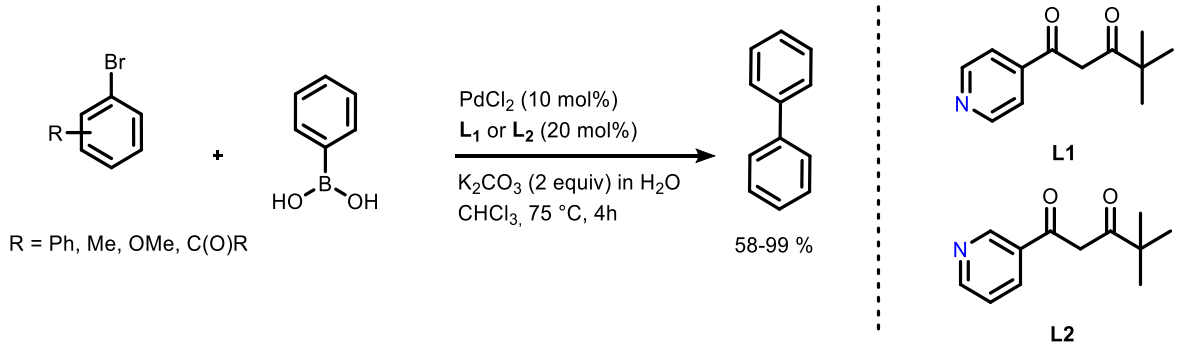
[113] A. Béziau, S. A. Baudron, M. W. Hosseini, *DaltonTrans*., **2012**, 41, 7227.

[114] M. J. Mayoral, P. Cornago, R. M. Claramunt, M. Cano, *New J. Chem.,* **2011**, 35, 1020.

[115] A. D. Burrows, M. F. Mahon, C. L. Renouf, C. Richardson, A. J. Warren, J. E. Warren, *DaltonTrans*., **2012**, 41, 4153.

[116] K. Banerjee, K. Biradha, *New J. Chem*., **2016**, 40, 1997.

Recently, Stefankiewiecz's group employed two simple ambidente pyridyl diketone ligands **L1** and **L2** in Suzuki-Miyaura coupling.[117] These two isomers differing by the diketone position on the pyridine moiety (*p* and *m* respectively) lead in the presence of catalytic amount of palladium dichloride to the reaction of aryl bromides with the phenylboronic acid to afford the expected coupling products with high selectivity and good yields (Scheme 60).



Scheme 60 : Suzuki-Miyaura coupling reaction catalyzed by $PdCl_2$ associated to pyridyl diketone ligands.

It is worthy to note that in presence of $PdCl_2$, the ligands **L1** and **L2** can form two different types of complexes, a neutral (**A**) and an ionic one (**B**). The authors showed by X-ray that depending on the conditions, the ligand-binding sites are able to exchange themselves. Indeed, basic or neutral conditions induce a switching between these two complexes (Figure 20) which thus behave as linkage isomers.

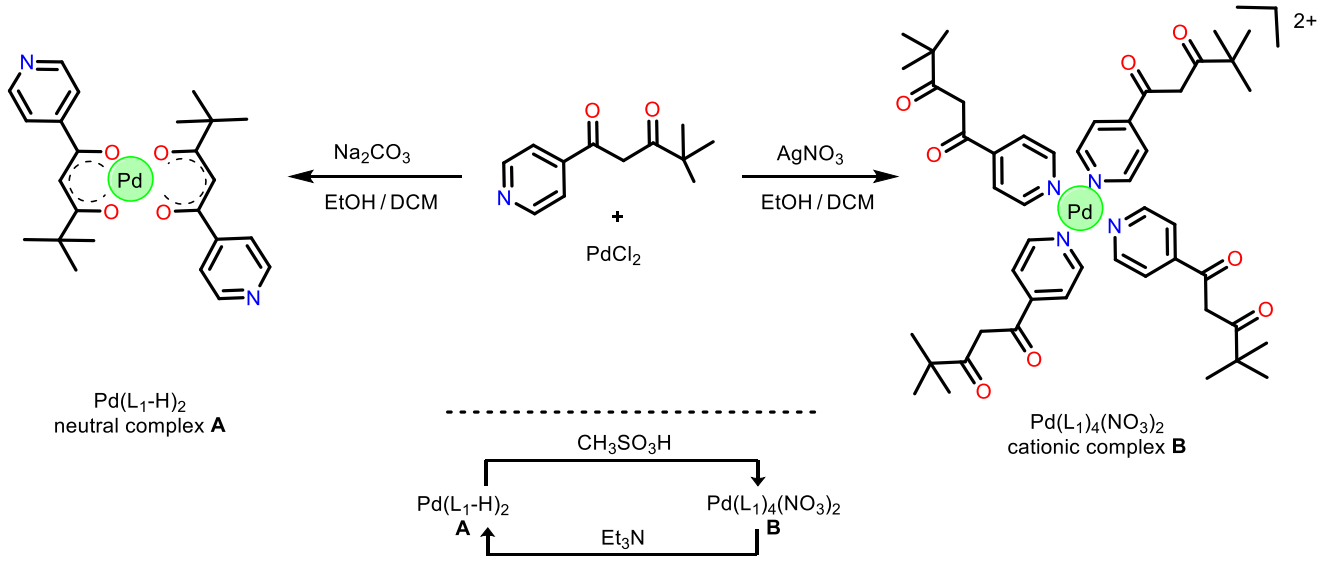
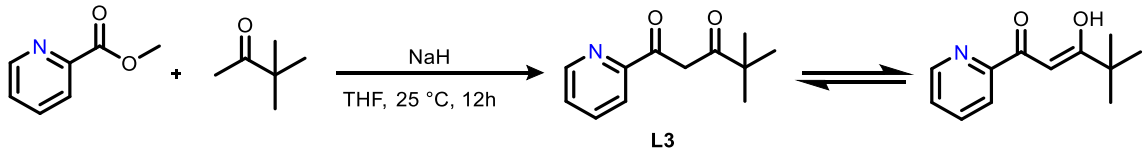


Figure 20 : neutral and cationic complexes for ligand **L1**.

Based on the previous result with the Suzuki-Miyaura cross-coupling reaction, the third isomer **L3** of these two ligands has been prepared by the authors in order to compare its reactivity to **L1** and **L2**. It was easily prepared in a similar way by Claisen condensation[117] between 3,3-dimethyl-2-butanone and the methyl 2-picolinate ester while using a strong base (Scheme 61).

[117] A. Walczak, A. R. Stefankiewicz. *Inorg. Chem.*, **2018**, 57, 471.



Scheme 61 : synthesis of ligand the **L3**.

Whereas, some pyridyl diketones have already been used as ligands in copper catalyzed arylation of nitrogen nucleophiles[118] such as sulfonamides and azole derivatives (imidazole, pyrrole and indole), it is not the case with **L1**, **L2** and **L3**. Moreover, there is not any example in the literature involving NH_3 as nucleophile regardless the type of pyridyl diketone ligands.

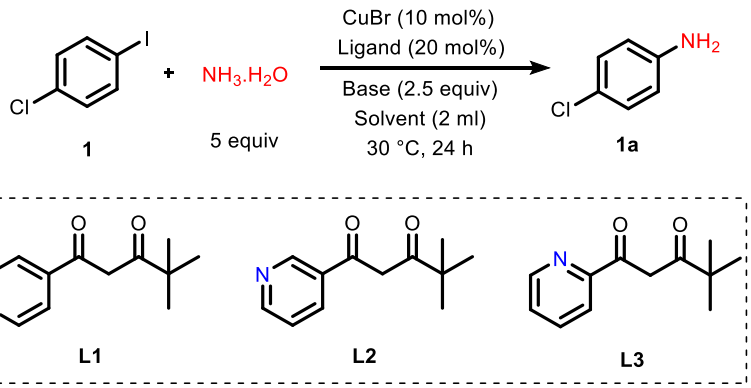
We thus, decided to test **L1**, **L2** and **L3** as ligands in copper catalyzed arylation of NH_3 with various aryl halides.

2. Copper catalyzed arylation of ammonia from aryl halides

a. From aryl iodides

We first tested pyridyl diketones as ligands for the copper catalyzed arylation of ammonia, using 4-chloro-iodobenzene as a model substrate.[91] Based on our team's previous work, we started the reaction by using 5 equivalents of aqueous ammonia, 10 mol % of CuBr and 20 mol % of the ligand (**L1**, **L2** or **L3**) at 30 °C for 24 h (Table 12). With cesium carbonate (Cs_2CO_3) used as base in DMF, we obtained selectively the 4-chloroaniline in almost identical yields for the 3 ligands (65, 66 or 64%; entries 1-3). The replacement of DMF by DMSO leads to a slight improvement in the yields (68, 75 and 75%; entries 4-6). The combination of tripotassium phosphate (K_3PO_4) with DMSO showed to be suitable for this reaction as the 4-chloroaniline was formed in this case with good to excellent yields (84, 94 and 95 %; entries 7-9). Note that using K_3PO_4 as base in DMF, the reaction affords the corresponding aniline with only poor to good yields (22, 68 and 71 %; entries 10-12). Thus in most cases, the three-ambident ligands gave good yields in 4-chloro-aniline at 30 °C. A test performed with **L3** at 25 °C gave **1a** in 87% of yield (entry 12). This reaction temperature constitute the limit below which the yields drop down.

Table 12 : variation of the amination conditons of 4-chloro-iodobenzene.



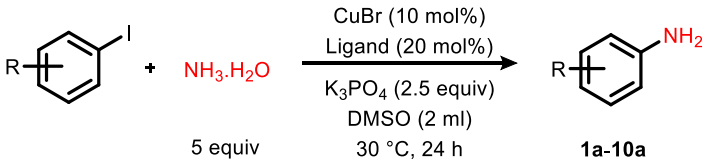
Entry	Base	Solvent	Ligand	Yield (%)[a]
1	Cs_2CO_3	DMF	L1	65
2	Cs_2CO_3	DMF	L2	66
3	Cs_2CO_3	DMF	L3	64

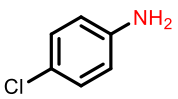
[118] a) Z. Xi, F. Liu, Y. Zhou, W. Chen, *Tetrahedron*, **2008**, 64, 4254. b) X. Han, *Tetrahedron Lett.*, **2010**, 51, 360.

4	Cs_2CO_3	DMSO	L1	68
5	Cs_2CO_3	DMSO	L2	75
6	Cs_2CO_3	DMSO	L3	75
7	K_3PO_4	DMSO	L1	84
8	K_3PO_4	DMSO	L2	94
9	**K_3PO_4**	**DMSO**	**L3**	**95**
10	K_3PO_4	DMF	L1	22
11	K_3PO_4	DMF	L2	68
12	K_3PO_4	DMF	L3	71
13[b]	**K_3PO_4**	**DMSO**	**L3**	**87**

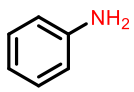
Reaction carried out with 1 mmol of 1, 5 mmol of $NH_3.H_2O$ (25%), 2.5 mmol of the base, 0.1 mmol of CuBr, 0.2 mmol of Ligand in 2 ml of solvent under an inert atmosphere, stirred for 24 hours at 30 °C. [a] Evaluated by 1H NMR with 1,3,5-trimethoxybenzene as internal standard. [b] Reaction carried out at 25 °C.

We then explored the application field of this sytem starting from various substituted aryl iodides, in the best conditions determined in the former study (entries 7-9, table 12) (Scheme 62). The reaction of the phenyl iodide with $NH_3.H_2O$ produced the aniline **2a** with 96 %, 93 %, and 85 % respectively with **L1**, **L2** and **L3**. The aryl iodides bearing electron-withdrawing group (EWG) such as *p*-nitro, *p*-cyano, *m*-trifluoromethyl and *p*-acetyl, afforded the corresponding anilines with good to excellent yields (**3a**, **4a**, **9a** and **10a** respectively). The arylation of ammonia from the 4-fluoroiodobenzene also proceeded successfully with the three ligands (**8a**). Electron rich aryl iodides such as 4-iodotoluene, 3-iodotoluene and 1-iodo-3,5-dimethylbenzene afforded the expected aniline derivatives with good to excellent yields (**5a**, **6a** and **7a** respectively). It should be noted that with almost all the substrates tested, the **L3** ligand gave the best yield (Scheme 62, **4a-10a**).

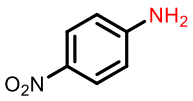




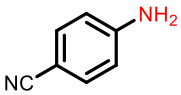
1 a
L1 84
L2 94
L3 95 (87)[a]



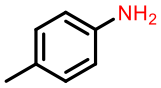
2 a
L1 96
L2 93
L3 85 (78)[a]



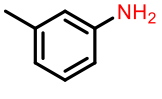
3 a
L1 67
L2 77
L3 61



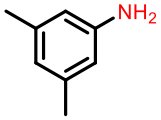
4 a
L1 80
L2 71
L3 87



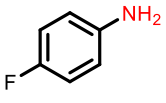
5 a
L1 76
L2 31
L3 79



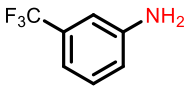
6 a
L1 71
L2 87
L3 94



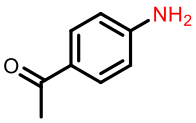
7 a
L1 95
L2 91
L3 93



8 a
L1 81
L2 71
L3 83 (71)[a]



9 a
L1 88
L2 80
L3 98



10 a
L1 99
L2 92
L3 98 (85)[a]

Reaction carried out with 1 mmol aryl iodide, 5 mmol of $NH_3.H_2O$ (25%), 2.5 mmol of the base, 0.1 mmol of CuBr, 0.2 mmol of Ligand in 2 ml of solvent under an inert atmosphere, stirred for 24 hours at 30 °C. Yield evaluated by ^1H NMR with 1,3,5-trimethoxybenzene as internal standard.[a] Reaction carried out at 25 °C.

Scheme 62 : copper-catalyzed amination of aryl iodides.

With some substrates, we also tested the reactivity of the catalytic system with the **L3** ligand at 25 ° C. The aniline derivatives are always obtained with good yields (87, 78, 71 and 85% respectively for **1a, 2a, 8a** and **10a**). This temperature constitutes a limit below which the yields drop down very quickly.

Some limitations appeared with this system based on CuBr and **L3**. Thus, in the case of 2-methyliodobenzene no reactivity was noticed, probably due to the steric hindrance of this substrate. In the case of 4-iodophenol, the system was not very effective at all (Figure 21).

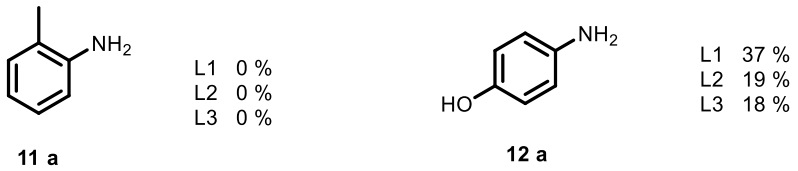


Figure 21 : reactivity limitations.

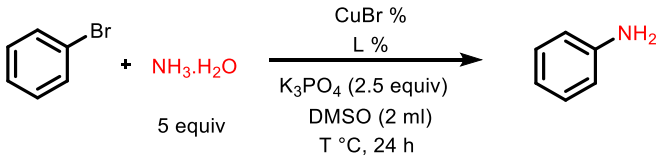
b. From aryl bromides

In a second time, we tested the system in the presence of aryl bromides. These substrates are usually less reactive than the corresponding aryl iodides but they are more interesting in terms of price and availability.

Starting from bromobenzene as a model substrate, we applied the best conditions used for the amination of aryl iodides but only traces of aniline were observed while bromobenzene was quantitatively recovered after 24h. Low yields were obtained at higher temperature than 30 °C (60 and 70 °C) with 10 mol% of CuBr and 20 mol% of ligand, whatever the type of the latter (**L1**, **L2** and **L3**) (Table 13, entries 1-6). At 80 °C, we obtained 50 % of the aniline with the ligand **L3**, while at 90 °C the yield decreased to 27 % (Entries 9 and 12). This unexplained result was repeated three times. Based on these results, we considered 80 °C (Entry 9) as the appropriate temperature and increased the catalytic loading of the copper while keeping same ratio of metal/ligand (1/2) (Entries 13-18).

We thus noticed that 15 mol% of CuBr and 30 mol% of **L3** are the best conditions to obtain a good yield of aniline at 80° C (Entry 15). Interestingly, **L1** and **L2** ligands were not very effective for the amination of bromobenzene (Entries 13-14).

Table 13 : variation of the experimental conditons for the amination of bromobenzene.

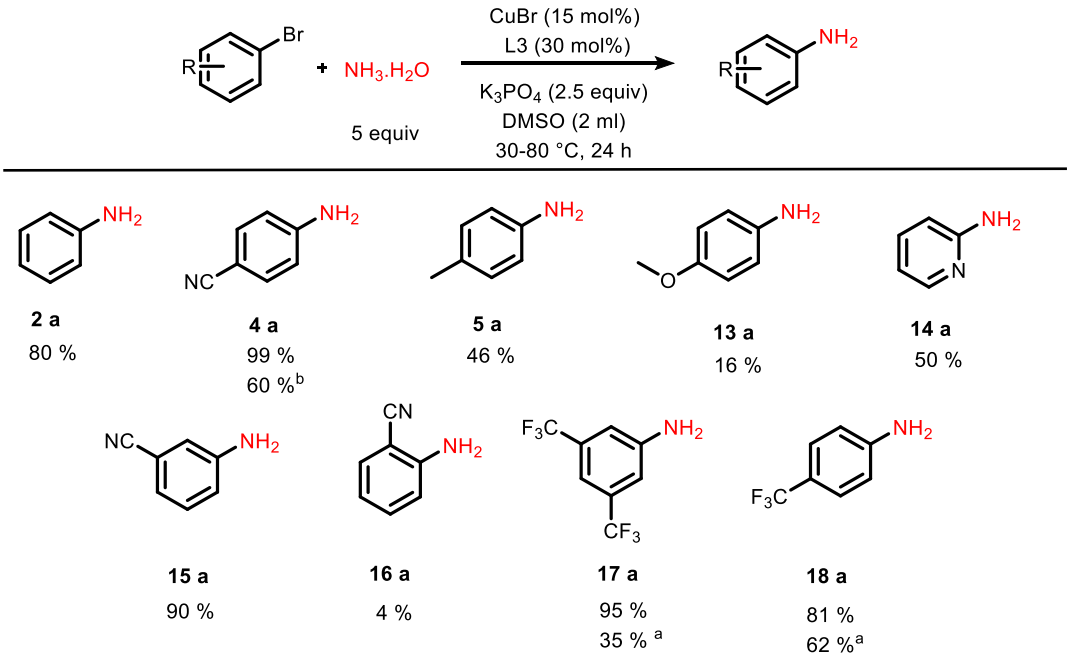


Entry	T (°C)	Ligand	CuBr (%)	L (%)	Yield (%)[a]
1	60	L1	10	20	0
2	60	L2	10	20	28
3	60	L3	10	20	41
4	70	L1	10	20	17
5	70	L2	10	20	35
6	70	L3	10	20	43
7	80	L1	10	20	17
8	80	L2	10	20	21

9	80	L3	10	20	50
10	90	L1	10	20	9
11	90	L2	10	20	14
12	90	L3	10	20	27
13	**80**	**L1**	**15**	**30**	**35**
14	**80**	**L2**	**15**	**30**	**36**
15	**80**	**L3**	**15**	**30**	**80**

Reaction carried out with 1 mmol of bromobenzene, 5 mmol of $NH_3.H_2O$ (25%), 2.5 mmol of the base, 0.1; 0.15 or 0.2 mmol CuBr, 0.2; 0.3 or 0.4 mmol of Ligand in 2 ml of solvent under an inert atmosphere, stirred for 24 hours at the indicated temperature. [a] Evaluated by ^1H NMR with 1,3,5-trimethoxybenzene as internal standard.

Based on these conditions, we tested a variety of aryl bromides (Scheme 63). With donor substituents on the aromatic cycle (*p*-iodotoluene **5a** and *p*-iodoanisole **13a**) low to medium yields were obtained (46 % and 16 % respectively). While using aryl bromides containing electron-withdrawing groups, such as *p*- and *m*-iodobenzonitrile, 1-iodo-3,5-bis(trifluoromethyl)benzene and *p*-trifluoromethybenzene, the corresponding anilines were obtained in good yields (**4a**, **15a**, **17a** and **18a** respectively 99 %, 90 %, 95% and 81%). On the other hand, the sterically crowded *o*-bromobenzonitrile was not suitable for this reaction as it affords only 4% of the desired product **16a**. A test realized with 2-bromopyridine afforded the 2-aminopyridine **14a** in moderate yield (50 %).

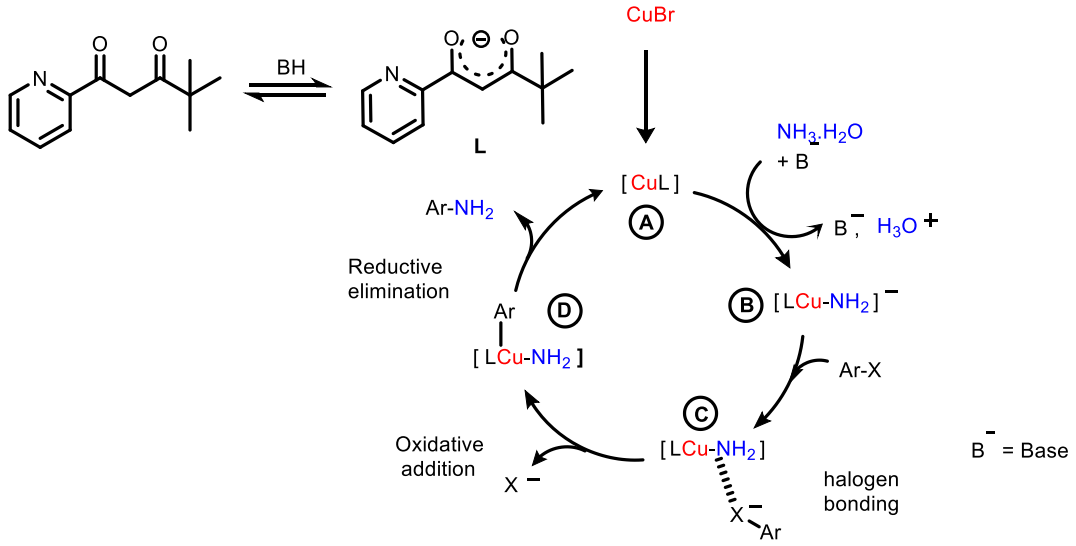


Reaction carried out with 1 mmol aryl bromide, 5 mmol of $NH_3.H_2O$ (25%), 2.5 mmol of the base, 0.15 mmol of CuBr, 0.3 mmol of L3 in 2 ml of solvent under an inert atmosphere, stirred for 24 hours. Yield Evaluated by 1H NMR with 1,3,5-trimethoxybenzene as internal standard. [a] Reaction carried out at 30 °C. [b] Reaction carried out at 40 °C

Scheme 63 : amination of aryls bromide derivatives.

Concerning the mechanism of the reaction, we did not realize a thoroughly study. However, based on former studies involving anionic copper catalyst for the arylation of *N*- and *O*-nucleophiles, we propose a mechanism in which the nucleophilic substitution takes place before the oxidative

addition.[119] Thus, we suggest that the ligand *in situ* coordinates to the metal to form Cu(L) as copper one species **A**, probably stabilized by the solvent (DMSO which is not represented in the catalytic cycle), which can react in presence of the base with ammonia to form **B** (Scheme 64). The presence of the aryl halide leads to the formation of the adduct **C** stabilized by the halogen bond. This precomplex would then undergo an oxidative addition with the aryl halide affording (Aryl)Cu(L)(NH_2) **D**, new copper (III) species, that could produce the coupled product after a reductive elimination step, also allowing the regeneration of the catalytic species.



Scheme 64 : proposed mechanism for aryl halide amination (solvent not represented).

3. Conclusion

In conclusion, we have developed a new copper catalytic system associated to a set of pyridyl diketones wich are simple and easily accessible ambident ligands. This system allowed to achieve the arylation of aqueous ammonia with aryl iodides derivatives, tolerating various substituents under very mild temperature conditions (25-30 °C). This method is also efficient for the arylation of various aryl bromides at 80 °C.[120] The high efficiency of the ligand **L3** could be connected to a simultaneous chelation of its two donor sites on the same metallic center.

Currently, we are testing these ligands in other type of coupling reaction in our laboratory.

[119] G. Lefèvre, G. Franc, A. Tlili, C. Adamo, M.Taillefer, I. Ciofini, A. Jutand. *Organometallics.* **2012**, 31, 7694.

[120] R. Abdine, G. Kurpik, A. Walczak, S. A. Aeash, A. R. Stefankiewicz, F. Monnier, M. Taillefer, *J. catal*. **2019**, 376, 119.

IV. Experimental part

1. General considerations

All reactions were performed in oven-dried Schlenk flasks under an atmosphere of argon closed with Rodavis® Screw caps. Copper bromide and tripotassium phosphate were purchased from Sigma-Aldrich®, used as received, stored in a desiccator cabinet and weighed to air. Ammonia solution 25% was purchased from Sigma-Aldrich® and used as received. Other reagents were purchased from either Sigma-Aldrich® or Alfa Aesar® or Acros Organics® and used as received.

^{1}H and ^{13}C NMR spectra were recorded with a Bruker AC-400 MHz spectrometer in $CDCl_3$ or DMSO-d_6. For ^{1}H NMR (400 MHz), $CHCl_3$ or DMSO and TMS served as internal standards (δ = 7.26 for $CHCl_3$, 2.50 for DMSO and 0 ppm for TMS) and data are reported as follows: chemical shift (in ppm), multiplicity (s = singlet, bs = broad singlet, d = doublet, t = triplet, q = quartet, dd = doublet of doublets, dt = doublet of triplets, td = triplet of doublets, ddd = doublet of doublet of doublets, m = multiplet), coupling constant (in Hz), and integration. For ^{13}C NMR (100 MHz), $CHCl_3$ or DMSO were used as internal standards (δ = 77.6 and 39.52 ppm) and spectra were obtained with complete proton decoupling. Gas chromatography–mass spectra (GC-MS) were recorded on a Shimadzu QP2012-SE with a Zebron ZB-5MS (20m × 0,18mm), capillary apolar column (Stationary phase: 0.18 µm film). GC-MS method: Initial temperature: 50°C; Initial time: 2 min; Ramp: 22°C/min; Final Temperature: 280°C; Final time: 15min or 23min. HRMS (Q-TOF) were performed on a JEOL JMS-DX300 spectrometer (3 keV, xenon) in a m-nitrobenzyl alcohol matrix. Melting points were measured using Stuart SMP50 Automatic Melting point.

2. General procedure for CuBr-catalyzed amination reaction of aryl iodides

After standard cycles of evacuation and back-filling with argon, an oven-dried Schlenk flask equipped with a magnetic stirring bar was charged with CuBr (0.1 mmol, 0.1 equiv), K_3PO_4 (2.5 mmol, 2.5 equiv) and solid aryl iodide (1 mmol, 1 equiv). The tube was evacuated and back-filled with argon. This procedure was repeated three times. Under a stream of argon, distilled DMSO (2.0 ml), aryl iodide (if liquid, 1 equiv), aqueous ammonia 25% (5 mmol, 5 equiv) and ligand (0.2 mmol, 0.2 equiv) were added by syringe. The Schlenk was sealed under a positive pressure of argon, stirred and heated at 30 °C for 24 h. Then 1,3,5-trimethoxybenzene (0.33 mmol, 0.33 equiv) was added as internal standard. The reaction mixture was diluted with dichloromethane and passed through a fritted glass filter, the filter cake being further washed with dichloromethane. The filtrate was washed with water. Gathered aqueous phase was extracted with dichloromethane for three times. The organic layers were collected, dried over $MgSO_4$, filtered and the solvent was removed under vacuum. The residue was purified by column chromatography on silica gel.

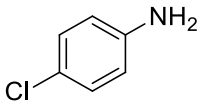
3. General procedure for CuBr-catalyzed amination reaction of aryl bromides

After standard cycles of evacuation and back-filling with argon, an oven-dried Schlenk flask equipped with a magnetic stirring bar was charged with CuBr (0.15 mmol, 0.15 equiv), K_3PO_4 (2.5 mmol, 2.5 equiv) and solid aryl bromide (1 mmol, 1 equiv). The tube was evacuated and back-filled with argon. This procedure was repeated three times. Under a stream of argon, distilled DMSO (2.0 ml), aryl bromide (if liquid, 1 equiv), aqueous ammonia 25% (5 mmol, 5 equiv) and ligand (0.3 mmol, 0.3 equiv)

were added by syringe. The Schlenk was sealed under a positive pressure of argon, stirred and heated at indicated temperature for 24 h. Then 1,3,5-trimethoxybenzene (0.33 mmol, 0.33 equiv) was added as internal standard. The reaction mixture was diluted with dichloromethane and passed through a fritted glass filter, the filter cake being further washed with dichloromethane. The filtrate was washed with water. Gathered aqueous phase was extracted with dichloromethane for three times. The organic layers were collected, dried over $MgSO_4$, filtered and the solvent was removed under vacuum. The residue was purified by column chromatography on silica gel. All products obtained by both procedures are known and described in the literature.

4. Experimental procedures and characterization data

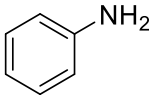
4-chloroaniline[95] **1a**



The reaction of 1-chloro-4-iodobenzene (1 mmol, 238.5 mg) according to the general procedure (flash chromatography pentane/ethyl acetate 90:10) gave the 4-chloroaniline **1a** in the form of pale yellow solid (79%, 101 mg).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.10 (d, J = 8.8 Hz, 2H), 6.60 (d, J = 8.8 Hz, 2H), 3.66 (bs, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 145.06, 129.24, 123.28, 116.34. HRMS (ESI) m/z: $[M+H]^+$ Calcd for C_6H_7ClN 128.0242; Found 128.0262. Melting point: 69 °C.

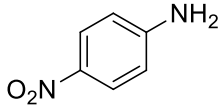
Aniline[91] **2a**



The reaction of iodobenzene (1 mmol, 112 µl) according to the general procedure (flash chromatography pentane/ethyl acetate 90:10) gave the aniline **2a** in the form of pale yellow liquid (79%, 74 mg).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.22 (t, *J* = 7.9 Hz, 2H), 6.82 (t, *J* = 6.3 Hz, 1H), 6.72 (d, *J* = 8.5 Hz, 2H), 3.67 (bs, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 146.33, 129.22, 118.44, 115.03. HRMS (ESI) m/z: $[M+H]^+$ Calcd for C_6H_8N 94.0651; Found 94.0652.

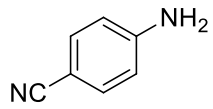
4-nitroaniline[91] **3a**



The reaction of 1-iodo-4-nitrobenzene (1 mmol, 249 mg) according to the general procedure (flash chromatography cyclohexane/ethyl acetate 90:10) gave the 4-nitroaniline **3a** in the form of yellow solid (72%, 99.5 mg).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.07 (d, *J* = 9.1 Hz, 1H), 6.62 (d, *J* = 9.1 Hz, 1H), 4.38 (s, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 152.37, 139.39, 126.45, 113.59. HRMS (ESI) m/z: $[M+H]^+$ Calcd for $C_6H_7N_2O_2$ 139.0508; Found 139.0509. Melting point: 146.2 °C.

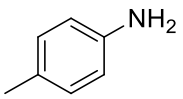
4-aminobenzonitrile[91] **4a**



The reaction of 4-idoobenzonitrile (1 mmol, 229 mg) according to the general procedure (flash chromatography cyclohexane/ethyl acetate 90:10 to 60:40) gave the 4-aminobenzonitrile **4a** in the form of white solid (81%, 96 mg).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39 (d, *J* = 8.8 Hz, 2H), 6.63 (d, *J* = 8.8 Hz, 2H), 4.21 (bs, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 150.61, 133.85, 120.32, 114.50, 99.97. HRMS (ESI) m/z: $[M+H]^+$ Calcd for $C_7H_7N_2$ 119.0604; Found 119.0609. Melting point: 86.5 °C.

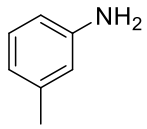
4-toluidine[91] **5a**



The reaction of 4-iodotoluene (1 mmol, 249 mg) according to the general procedure (flash chromatography pentane/ethyl acetate 80:20) gave the 4-toluidine **5a** in the form of yellow solid (67 %, 72 mg).

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.97 (d, J = 8.2 Hz, 2H), 6.61 (d, J = 8.2 Hz, 2H), 3.54 (bs, 2H), 2.24 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 143.92, 129.89, 127.94, 115.40, 20.60. HRMS (ESI) m/z: $[M+H]^+$ Calcd for $C_7H_{10}N$ 108.0769; Found 108.0808. Melting point: 45.9 °C.

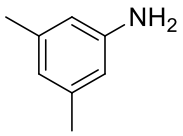
3-toluidine[93] **6a**



The reaction of 3-iodotoluene (1 mmol, 128 µl) according to the general procedure (flash chromatography cyclohexane/ethyl acetate 80:20) gave the 3-toluidine **6a** in the form of colourless liquid (78 %, 83 mg).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.04 (t, *J* = 7.6 Hz, 1H), 6.57 (d, *J* = 7.6 Hz, 1H), 6.51 – 6.46 (m, 2H), 3.57 (bs, 2H), 2.27 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 142.94, 138.88, 129.07, 121.34, 118.23, 114.64, 21.73. HRMS (ESI) m/z: $[M+H]^+$ Calcd for $C_7H_{10}N$ 108.0783; Found 108.0808.

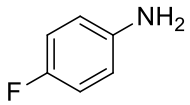
3,5-dimethylaniline[95] 7a



The reaction of 1-iodo-3,5-dimethylbenzene (1 mmol, 144 µl) according to the general procedure (flash chromatography pentane/ethyl acetate 90:10) gave the 3,5-dimethylaniline **8a** in the form of brown oil (78%, 94 mg).

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.43 (s, 1H), 6.34 (s, 2H), 3.56 (bs, 2H), 2.23 (s, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 146.43, 139.11, 120.59, 113.19, 21.42. HRMS (ESI) m/z: $[M+H]^+$ Calcd for $C_8H_{12}N$ 122.0964; Found 122.0969.

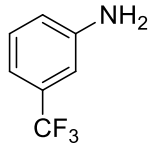
4-fluoroaniline 8a



The reaction of 1-fluoro-4-iodobenzene (1 mmol, 115 µl) according to the general procedure (flash chromatography pentane/ethyl acetate 90:10) gave the 4-fluoroaniline **9a** in the form of brown liquid (67%, 75 mg).

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.89 – 6.82 (m, 2H), 6.66 – 6.59 (m, 2H), 3.51 (bs, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 157.75, 155.40, 142.50, 115.70. HRMS (ESI) m/z: $[M+H]^+$ Calcd for C_6H_7FN 112.0546; Found 112.0557.

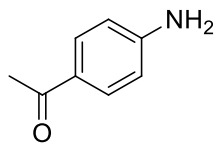
3-(trifluoromethyl)aniline[93] 9a



The reaction of 3-iodobenzotrifluoride (1 mmol, 145 µl) according to the general procedure (flash chromatography pentane/ethyl acetate 90:10) gave the 3-(trifluoromethyl)aniline **10a** in the form of colourless liquid (81%, 130 mg).

^{1}H NMR (400 MHz, DMSO-d_6) δ 7.19 (t, J = 7.9 Hz, 1H), 6.85 (s, 1H), 6.80 (d, J = 8.1 Hz, 1H), 6.76 (d, J = 8.5 Hz, 1H), 5.55 (bs, 2H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 149.42, 129.83 (q, J = 28.7 Hz), 125.94 , 123.24 , 117.24, 111.43, 109.45. HRMS (ESI) m/z: $[M+H]^+$ Calcd for $C_7H_7F_3N$ 162.0525; Found 162.0565.

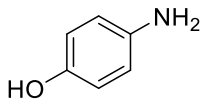
4-aminoacetophenone[91] 10a



The reaction of 4-iodoacetophenone (1 mmol, 246 mg) according to the general procedure (flash chromatography pentane/ethyl acetate 90:10 to 50:50) gave the 4-aminoacetophenone **11a** in the form of light orange solid (93%, 125.5 mg).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.81 (d, *J* = 8.8 Hz, 2H), 6.65 (d, *J* = 8.8 Hz, 2H), 4.13 (bs, 2H), 2.51 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 196.50, 151.10, 130.84, 127.96, 113.76, 26.13. HRMS (ESI) m/z: $[M+H]^+$ Calcd for $C_8H_{10}NO$ 136.0757; Found 136.0769. Melting Point: 104.2 °C.

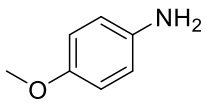
4-aminophenol 12a



The reaction of 4-iodophenol (1 mmol, 220 mg) according to the general procedure (flash chromatography pentane/ethyl acetate 90:10) gave the 4-aminophenol **12a** in the form of brown solid (12%, 13 mg).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.09 (s, 1H), 6.67 (d, *J* = 8.9 Hz, 2H), 6.60 (d, *J* = 8.9 Hz, 2H), 4.68 (s, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 149.40, 142.16, 116.61, 116.13. HRMS (ESI) m/z: $[M+H]^+$ Calcd for C_6H_8NO 110.0606; Found 110.0604. Melting point: 187°C.

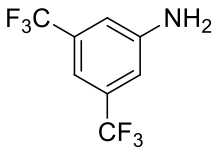
***p*-anisidine[91] 13a**



The reaction of 4-bromoanisole (1 mmol, 125 µl) according to the general procedure (flash chromatography pentane/ethyl acetate 70:30) gave the p-anisidine **13a** in the form of brown solid (11%, 14 mg).

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.74 (d, *J* = 9.0 Hz, 2H), 6.65 (d, *J* = 9.0 Hz, 2H), 3.74 (s, 3H), 3.42 (bs, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 152.83, 139.92, 116.46, 114.81, 55.76. HRMS (ESI) m/z: $[M+H]^+$ Calcd for $C_7H_{10}NO$ 124.0762; Found 124.0761. Melting point: 61°C.

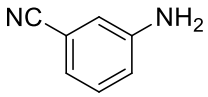
3,5-bis(trifluoromethyl)aniline 17a



The reaction of 1,3-bis(trifluoromethyl)-5-bromobenzene (1 mmol, 172 µl) according to the general procedure (flash chromatography hexane/ethyl acetate 80:20) gave the 3,5-bis(trifluoromethyl)aniline **16a** in the form of light yellow liquid (83%, 191 mg).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.21 (s, 1H), 7.03 (s, 2H), 4.07 (bs, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 147.47 , 132.69 (q, *J* = 33.0 Hz), 123.55 (d, *J* = 272.5 Hz), 114.31 (d, *J* = 4.9 Hz), 112.88 – 108.50 (m). HRMS (ESI) m/z: $[M+H]^+$ Calcd for $C_8H_6F_6N$ 230.0411; Found 230.0399.

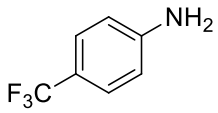
3-aminobenzonitrile 15a



The reaction of 3-bromobenzonitrile (1 mmol, 182 mg) according to the general procedure (flash chromatography cyclohexane/ethyl acetate 90:10 to 70:30) gave the 4-aminobenzonitrile **18a** in the form of light brown solid (80%, 83 mg).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.20 (t, J = 7.9 Hz, 1H), 6.99 (dt, J = 7.6, 1.3 Hz, 1H), 6.91 – 6.81 (m, 2H), 3.92 (s, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 147.09, 130.12, 121.96, 119.29, 117.47, 112.89. HRMS (ESI) m/z: $[M+H]^+$ Calcd for $C_7H_7N_2$ 119.0604; Found 119.0609. Melting point: 54.1 °C

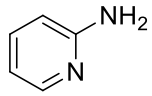
4-(trifluoromethyl)aniline[93] **18a**



The reaction of 4-bromobenzotrifluoride (1 mmol, 138 µl) according to the general procedure (flash chromatography hexane/ethyl acetate 90:10) gave the 4-(trifluoromethyl)aniline **20a** in the form of yellow liquid (73%, 117 mg).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39 (d, *J* = 8.4 Hz, 1H), 6.68 (d, *J* = 8.3 Hz, 1H), 3.95 (s, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 149.32, 126.80, 126.28, 123.66, 114.26.HRMS (ESI) m/z: $[M+H]^+$ Calcd for $C_7H_7F_3N$ 162.0525; Found 162.0563.

2-aminopyridine[91] **14a**



The reaction of 2-bromopyridine (1 mmol, 95 µl) according to the general procedure (flash chromatography pentane/ethyl acetate 90:10) gave the 2-aminopyridine **21a** in the form of yellow solid (47%, 45mg).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.11 – 8.02 (m, 1H), 7.51 – 7.31 (m, 1H), 6.71 – 6.55 (m, 1H), 6.48 (dd, *J* = 7.7, 4.1 Hz, 1H), 4.48 (bs, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 158.58, 148.21, 137.81, 114.08, 108.71. HRMS (ESI) m/z: $[M+H]^+$ Calcd for $C_5H_7N_2$ 95.0574; Found 95.0604. Melting point: 60.5 °C.

Chapter III:

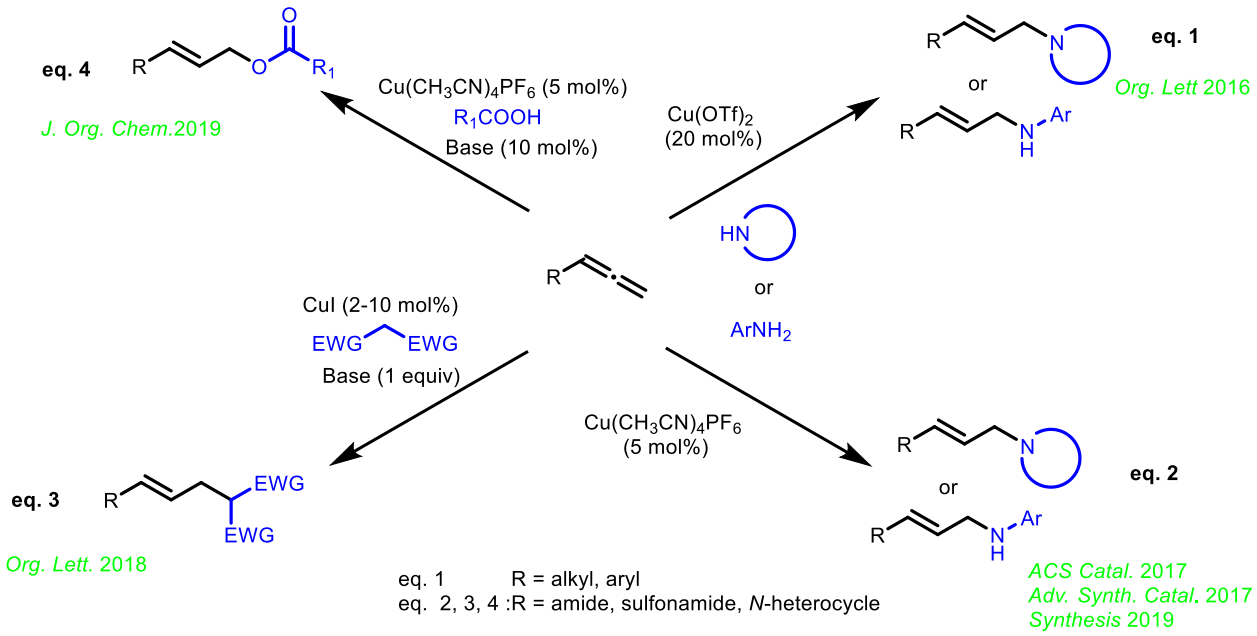
Copper-catalyzed intermolecular hydrofunctionalization of allenes

I. Introduction: allenes and functionalizations

Allene is a molecule including a function of three contiguous carbon atoms forming 1,2-diene skeleton. In many cases, allenes were widely used as key intermediates for the synthesis of pharmaceutical compounds.[121]

In the last decades, allene functionalization has gained a particular attention, due to the variety of compounds that can be transformed, with a high atom economy. Many transition metals have been involved in inter- and intramolecular allene functionalizations. In this chapter, we get interested in one family of functionalization: the hydrofunctionalization of allenes.

Recently, our laboratory developed new methods for the hydrofunctionalization of allenes with high regio- and stereoselectivities by using copper as catalyst, which is a cheap, abundant and low toxic metal (Scheme 65).



Scheme 65 : copper-catalyzed hydrofunctionalizations of allenes achieved in the laboratory.

In 2016, the hydroamination of aryl and alkyl allene has been achieved with secondary cyclic amines and anilines by using 20 mol% of $Cu(OTf)_2$.[122] The corresponding allylic amines have been obtained regio- and stereoselectively with moderate to excellent yields (eq. 1). This type of functionalization was later extended and applied to other families of allenes, with a diversification of amines. By using 5 mol% of $Cu(CH_3CN)_4PF_6$, the hydroamination of allene amides[123], sulfonamides[124] and *N*-heterocycles[125] derivatives was achieved with high regio- and stereoselectivities under milder conditions (eq. 2). A mechanistic study was realized to explain this selectivity, and showed the chelating assistance of the amide oxygen to the copper center (Figure 21). Due to this coordination,

[121] S. Yu, S. Ma, *Angew. Chem. Int. Ed.* **2012**, 51, 3074.
[122] R. Blieck, J. Bahri, M. Taillefer, F. Monnier, *Org. Lett.* **2016**, 18, 1482.
[123] L. A. Perego, R. Blieck, A. Groué, F. Monnier, M. Taillefer, I. Ciofini, L. Grimaud, *ACS Catal.* **2017**, 7, 4253.
[124] R. Blieck, L. A. Perego, I. Ciofini, L. Grimaud, M. Taillefer, F. Monnier, *Synthesis*. **2019**, 51, 1225.
[125] L. A. Perego, R. Blieck, J. Michel, I. Ciofini, L. Grimaud, M. Taillefer, F. Monnier, *Adv. Synth. Catal*. **2017**, 359, 4388.

the anti periplaner attack of the cyclic amine affords selectively the *E*-allylic amine. This chelation effect explains the high reactivity of the allenamide derivatives.

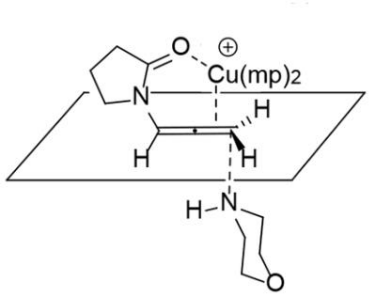


Figure 22 : transition state of morpholine's attack on activated allenamide.

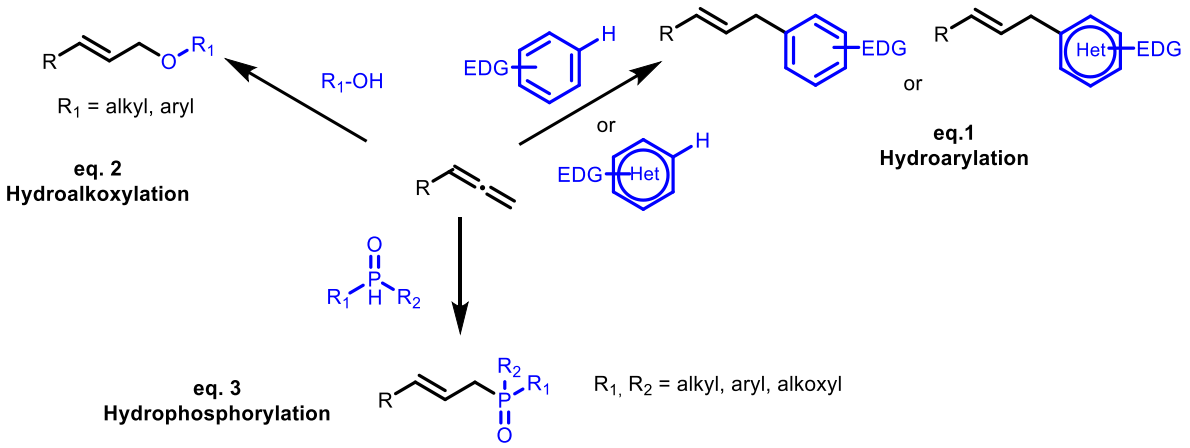
Then, we elaborated the creation of C-C bonds by a selective addition of carbon pronucleophiles.[126] In presence of stoichiometric amount of base, we realized a selective allylation of dicarbonyl compounds such as malonates, diketones and ketoesters by using 2 to 10 mol% of copper iodide (eq. 3). This reaction afforded the *E*-allylic product with a total atom economy.

In order to extend this method on different type of nucleophiles, the addition of carboxylic acid was performed in presence of 5 mol% of $Cu(CH_3CN)_4PF_6$ and catalytic amount of base (eq. 4). This method led to the formation of new C-O bond *via* a selective hydrocarboxylation of *N*-allene derivatives.[127] The corresponding allylic esters were obtained selectively in fair to excellent yields.

Currently in our laboratory, we are interested on the extension of the copper-catalyzed hydrofunctionalization of allenes to other nucleophiles to create a wide variety of selective bonds in order to afford valuable allylic products.

In this chapter we present three new methodologies that we are still working on (Scheme 66). First, we developed a new system for the direct hydroarylation of allenes with electron-rich aryls or heteroaromatics (eq. 1). We optimized the corresponding conditions, and we are currently finishing the scope. The two following reactions consist on the creation of C-heteroatom bonds : the hydroalkoxylation by the addition of alcohols (eq. 2) and the hydrophosphorylation by using phosphine oxide as nucleophiles (eq. 3).

[126] R. Blieck, R. A. Abdine, M. Taillefer, F. Monnier, *Org. Lett*. **2018**, 20, 2232.
[127] R. Blieck, M. Taillefer, F. Monnier, *J. Org. Chem*. 2**019**, 84, 11247.



Scheme 66 : copper-catalyzed hydrofunctionalizations of allene in progress in the laboratory.

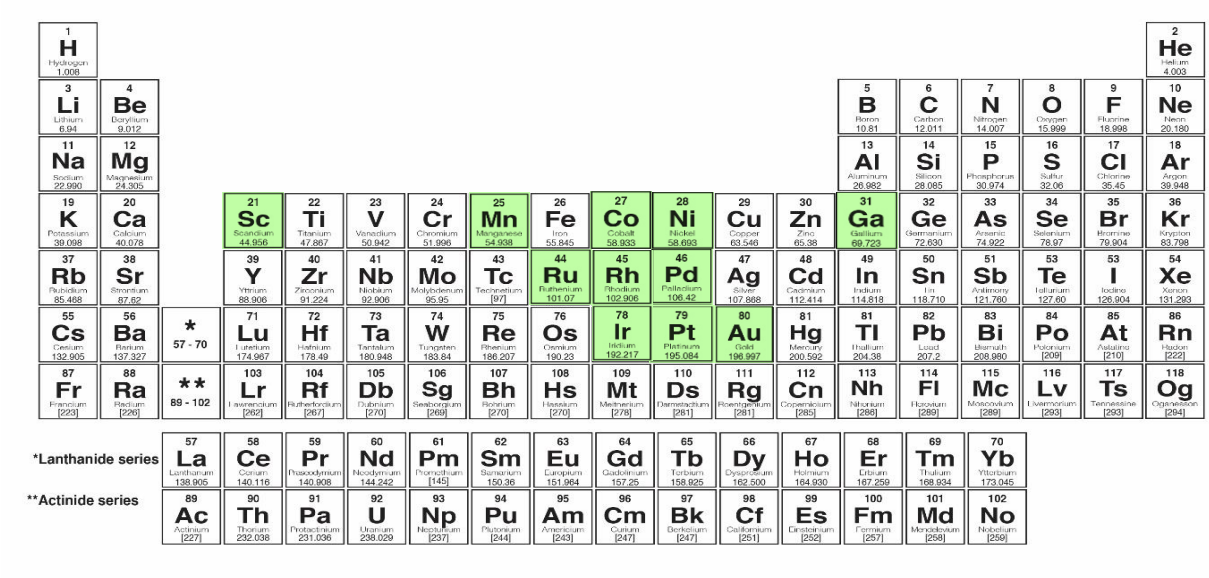
II. Intermolecular hydroarylation of allenes

1. Allenes hydroarylation promoted by metals: state of the art

One of the methods to generate new C-C bond through allenes is hydroarylation. This reaction occurs by metal catalysis (Scheme 67). There are two main strategies for the hydroarylation: the direct one promoted by C-H functionalization and the second one consists on the addition of boronic acids or other intermediates.

Scheme 67 : metal-catalyzed hydroarylation of allenes.

a. Direct Hydroarylation

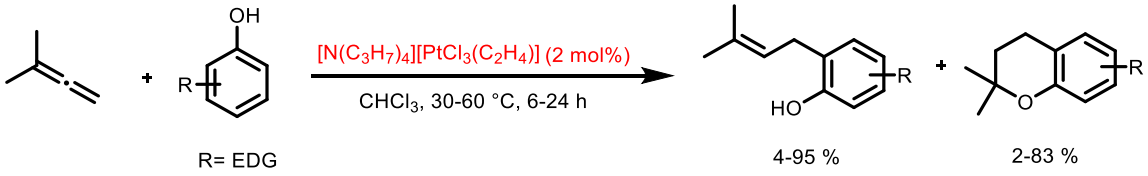


Since the beginning of 80's several metals have been used to promote the addition of the aromatics on allenes. Herein, we cite the reported researches on hydroarylation by metal's family:

- Platinum

Panunzi's group was the first to disclose in 1983 the addition of phenols on 1,1-dimethylallene.[128] Using platinum complex (II) as catalyst, the allylic product was formed with high regioselectivity and the addition occurred in the *ortho* position of the phenol hydroxyl group. The reaction is limited to electron rich phenols and leads in the most of cases to the formation of 2,2-dimethylchromane, after cyclization of the main one (Scheme 68).

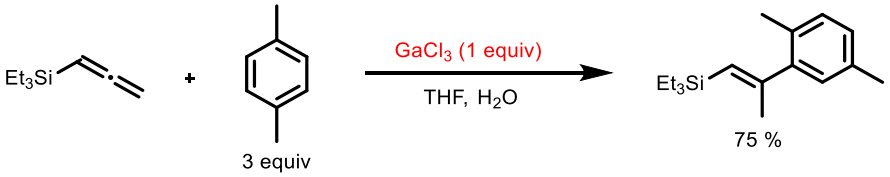
[128] A. De Renzi, A. Panunzi, A. Saporito, A. Vitagliano. *J. Chem. Soc. Perkin trans*. **1983**, 2, 993.



Scheme 68 : platinium-catalyzed hydroarylation of 1,1-dimethylallene.

- Gallium

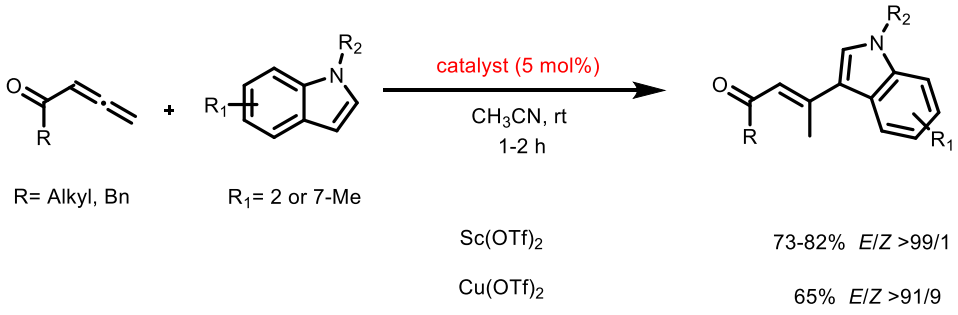
A post transition metal has been engaged in the intermolecular hydroarylation of allene. In 2001, Yamaguchi's group used a stoichiometric amount of $GaCl_3$ to promote the hydroarylation of 1-triethylsilyl-1,2-propadiene with *p*-xylene.[129] The addition occurs selectively in the central carbon to afford the vinyl product with 75% of yield (Scheme 69).



Scheme 69 : hydroarylation of allenylsilane promoted by gallium.

- Scandium

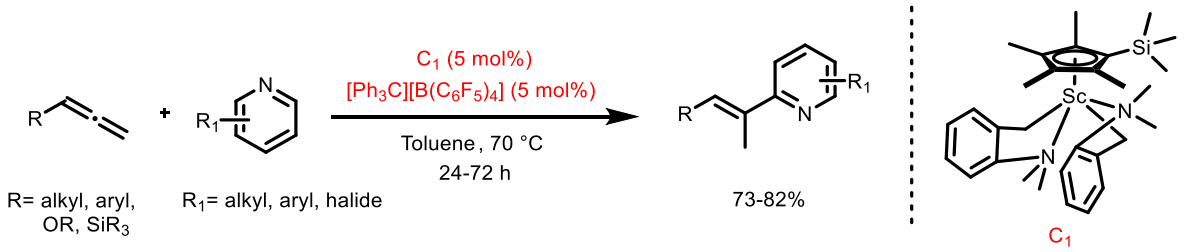
In 2005, Ma's group described the hydroarylation of allenic ketones with indole derivatives by using catalytic amount of scandium triflate under mild conditions to obtain vinyl indole derivatives (Scheme 76). The authors mentioned in their conditions optimization a test with 5 mol% of copper triflate, which afforded a good yield of the branched product (65%) but with low *E*/*Z* ratio (91/9).[130]



Scheme 70 : scandium-catalyzed hydroindolyllation

This rare-earth metal has been also used by Hou and coworkers in 2015 to realize the C-H alkenylation of several pyridines with terminal allenes.[131] The corresponding branched alkenylated product is formed by using half sandwich scandium **C₁** and $[Ph_3C][B(C_6F_5)_4]$ as catalysts. This method tolerates many functional groups especially on the allene skeleton (Scheme 71).

[129] Y. Kido, F. Yonehara, M. Yamaguchi, *Tetrahedron*, **2001**, 57, 827.
[130] S. Ma, S. Yu. *Org. Lett.*, **2005**, 7, 5063.
[131] G. Song, B. Wang, M. Nishiura, Z. Hou. *Chem. Eur. J.* **2015**, 21, 8394.

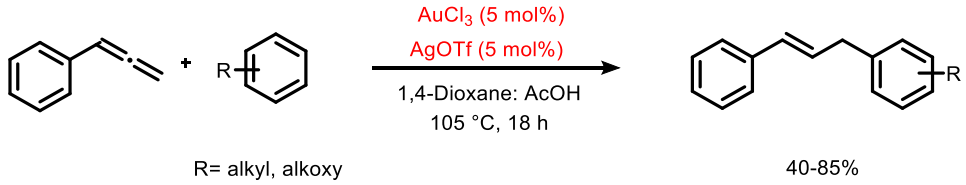


Scheme 71 : scandium-catalyzed addition of pyridine derivatives to allenes.

- Gold

Among all the metals, gold has been the most used for the hydroarylation of allenes as gold-based catalysts are known to activate C-H bonds.

In 2008, Li's group reported the first gold-catalyzed addition of substituted benzenes to phenylallene.[132] In presence of catalytic quantity of silver salt, the reaction occurs with total regioselective addition on the allene terminal carbon (Scheme 72). The aryl addition occurred in the most of the cases on the *ortho* position of the R substituent.

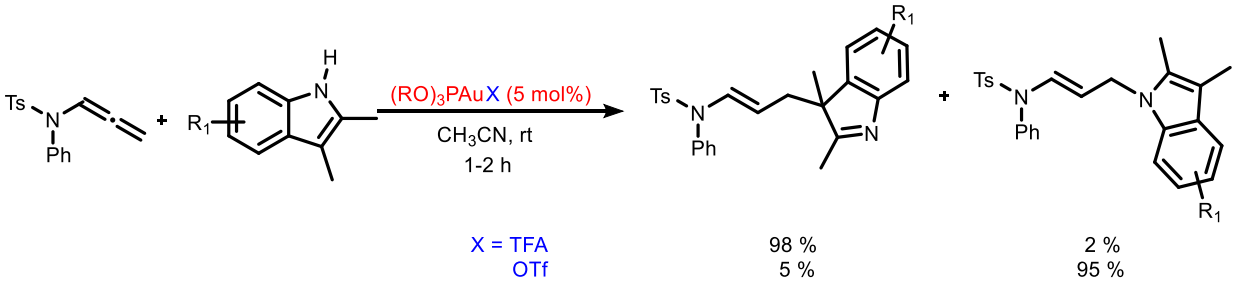


Scheme 72 : gold-catalyzed hydroarylation of phenylallene.

Using the same catalytic system associated to NHC ligand, Widenhoefer's group realized one year later the hydroarylation of terminal, 1,3-disubstituted and 1,1,3,3-tetrasubstitued allenes with heteroaromatics mainly the 1,2-dimethylindole. The reaction was carried out at 23°C, for 2-48h.[133]

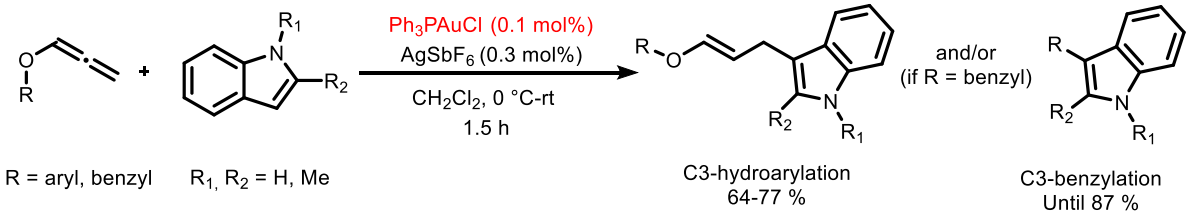
In the following years, other groups studied the hydroindolylation of terminal allenes. Bandini's group achieved the selective addition of indoles on the allenamide terminal carbon. Depending on the counterion of the gold catalyst, the chemoselectivity of this reaction changes. In presence of trifluoroacetic ions, the addition happened on the C3 position and it may be followed by a de-aromatization due to a coordinating ability and hydrogen-bonding tendency of the counterion. While using triflic ion, the main product resulted from the nucleophilic attack of the indol nitrogen atom on the allene (Scheme 73).[134]

[132] R. Skouta, C.-J. Li, *Can. J. Chem*., **2008**, 86, 616.
[133] K. L. Toups, G.T. Liu, R.A. Widenhoefer, *J. Organomet. Chem*. **2009**, 694, 571.
[134] a) M. Jia, G. Cera, D. Perrotta, M. Monari, M. Bandini, *Chem. Eur. J*. **2014**, 20, 9875. b) L. Rocchigiani, M. Jia, M. Bandini, A. Macchioni, *ACS Catal*. **2015**, 5, 3911.



Scheme 73 : the counterion effect on the hydroindolylation of allene sulfonamide.

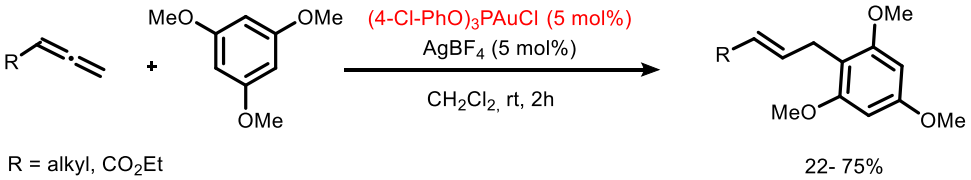
Likewise, Ramana and co-workers developed the hydroindolylation of allenyl ether.[135] With catalytic quantity of gold and $AgSbF_6$, they obtained the allylic product in moderate to good yields. These reaction conditions suffer from a bad chemoselectivity: when R is a benzyl derivatives, the reaction affords in some cases C3-benzylated compound as secondary or even as the only product (Scheme 74).



Scheme 74 : gold-catalyzed hydroindolylation of allenyl ether.

Che and co-workers studied the enantioselective addition of indoles to 1,3-disubstitued allenes.[136] With chiral biaryl phosphine as best ligand, they obtained poor to modest enantiomeric excess. While recently, Lee's group controlled the enantiomeric ratio of this reaction, however the main drawback was the regioselectivity of the (hetero) aromatic addition.[137]

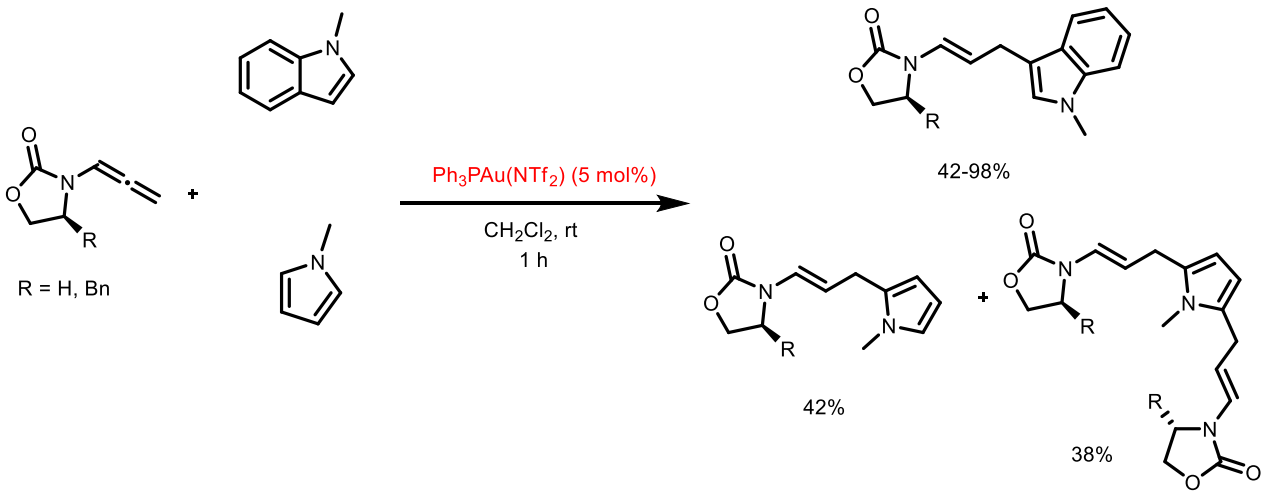
In 2009 Gagné's group described the hydroarylation of allenes by using gold and silver catalytic system.[138] The scope was limited to five examples of electron rich arenes containing both *ortho*- and *para*-directing groups (Scheme 75).



Scheme 75 : addition of electron rich arenes to allene using gold based catalytic system.

One year later, Kimber developed the addition of the indole on allenamide (Scheme 76).[139] Even though this reaction is carried out under mild and smooth conditions, it was not selective and not general: it was not regioselective and it affords the double addition on some heteroaromatics (for instance furane and *N*-methyl-pyrrole).

[135] C. Naidu Kona, M. H. Shinde, C. V. Ramana, *Org. Biomol. Chem.*, **2015**, 13, 5358.
[136] M. -Z. Wang, C.-Y. Zhou, Z. Guo, E. L.-M. Wong, M.-K. Wong, C.-M. Che, *Chem. Asian J.* **2011**, 6, 812.
[137] D. S. Sutherland, L. Kinsman, S. M. Angiolini, G. M. Rosair, A.-L. Lee, *Chem. Eur. J.* **2018**, 24, 7002.
[138] M. A. Tarselli, A. Liu, M. R. Gagné, *Tetrahedron*, **2009**, 65, 1785.
[139] M. C. Kimber, *Org. Lett.* **2010**, 12, 1128.

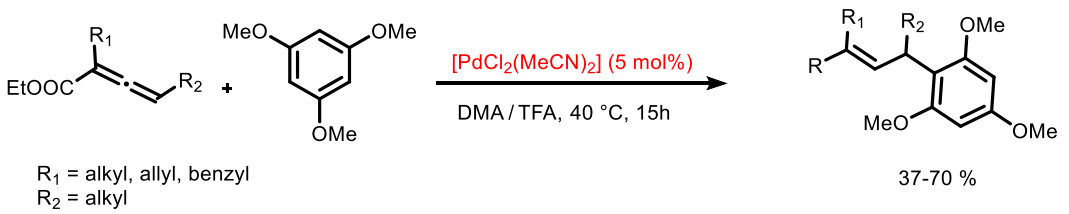


Scheme 76 : gold-catalyzed hydroindolylation of allenamide.

- Palladium :

In parallel to the numerous applications of gold catalytic systems in allene's hydroarylation, other metals have been used timidly in this reaction.

Ma's group was the only one to develop palladium-catalytic system for the hydroarylation of 2,3-allenoates with electron rich alkoxy arenes.[140] They applied their method on three arenes: 1,3,5-trimethoxybenzene, phenol and anisole (Scheme 77). The reaction was carried out at 40 °C in trifluoroacetic acid (TFA) in presence of dimethyl acetamide (DMA), to afford selectively the corresponding *E*-allylic product.

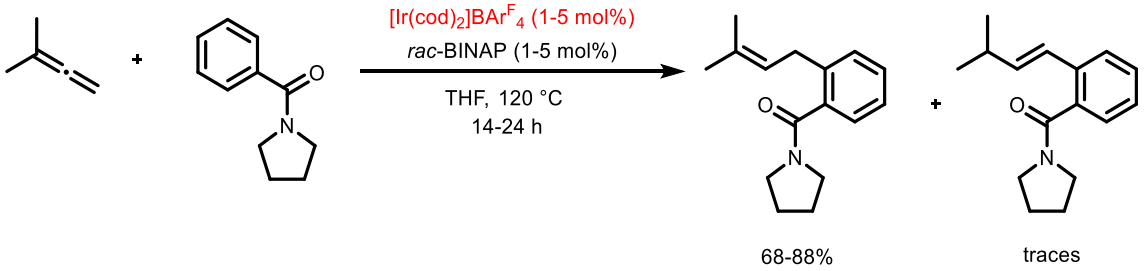


Scheme 77 : palladium-catalyzed hydroarylation of 2,3-allenoates.

- Iridium

Another example of the rarely employed metal in the hydroarylation, is the iridium. The latter was used by Krische to realize the addition of aromatics and heteroaromatics carboxamides to 1,1-dimethylallene. [141] This reaction occurs at 120 °C in the presence of iridium-catalyst and a diphosphine ligand (Scheme 78).

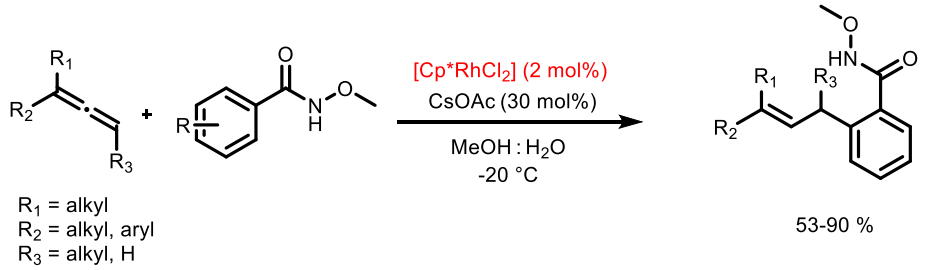
[140] Z. Fang, C. Fu, S. Ma, *Chem. Eur. J*. **2010**, 16, 3910.
[141] Y. J. Zhang, E. Skucas, M. J. Krische, *Org. lett.* **2009**, 11, 4248.



Scheme 78 : iridium-catalyzed hydroarylation of 1,1-dimethylallene.

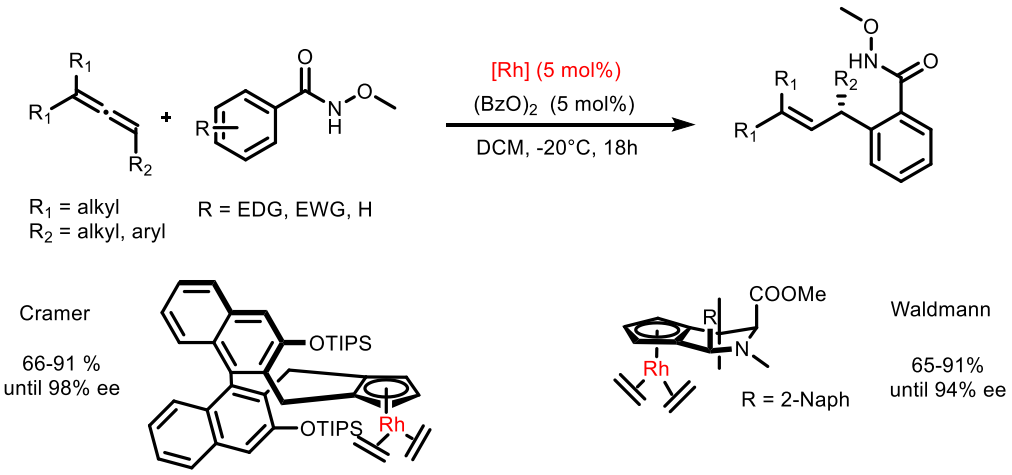
- Rhodium

In 2012, Ma's group described the first addition of *N*-methoxybenzamide to 1,1-disubstituted and 1,1,3-trisubstituted allenes by using a rhodium-based catalytic system (Scheme 79).[142] This hydroarylation occurs selectively on the terminal carbon of the allene.



Scheme 79 : rhodium-catalyzed hydroarylation of allenes with *N*-methoxybenzamide.

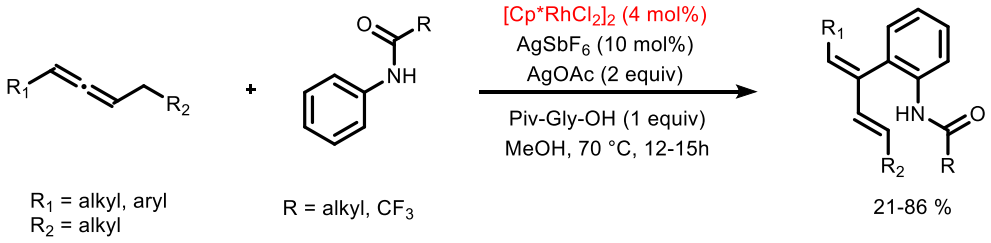
Later, two different chiral cyclopentadienyl ligands have been developed separately by Cramer[143] and Waldmann[144] performing two efficient enantioselective rhodium-based catalytic systems for the hydroarylation of allenes with benzamides derivatives (Scheme 80). A catalytic amount of dibenzoyl peroxide was necessary in both examples to oxidize the Rh (I) to Rh (III) which is the active catalytic specie that can promote the C_{Ar}-H allylation.



Scheme 80 : enantioselective allylation of benzamide by Rh-catalytic system.

[142] R. Zeng, C. Fu, S. Ma, *J. Am. Chem. Soc.* **2012**, 134, 9597.
[143] B. Ye, N. Cramer, *J. Am. Chem. Soc.* **2013**, 135, 636.
[144] Z.-J. Jia, C. Merten, R. Gontla, C. G. Daniliuc, P. Antonchick, H. Waldmann, *Angew. Chem. Int. Ed*, **2017**, 56, 2429.

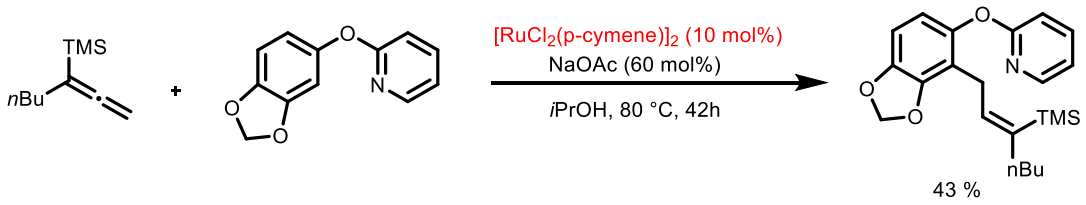
Recently, Ghosh and coworkers reported a rhodium-catalyzed hydroarylation of allenes with anilide derivatives.[145] This reaction was carried out in presence of silver acetate, which serves as oxidative regenerator for the catalyst active specie. The aryl insertion on the central carbon was followed by β-hydride elimination to release the corresponding diene in low to good yields (Scheme 81).



Scheme 81 : rhodium-catalyzed dienylation of anilides.

- Ruthenium

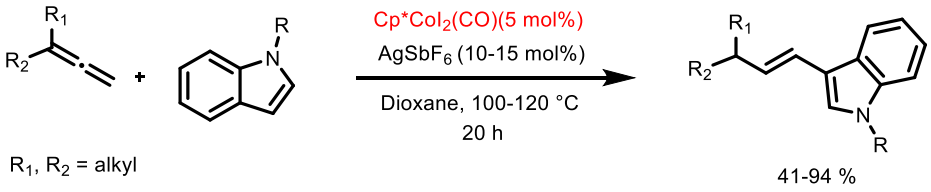
In 2015, Ackermann described a ruthenium-catalyzed allenylation of aromatics.[146] In this study, authors reported a single example about the hydroarylation of a gem disubstituted silylallene. This selective reaction yields the allylic aryl with 43% of yield (Scheme 82).



Scheme 82 : ruthenium-catalyzed hydroarylaion of 1,1-disubstituted allene.

- Cobalt

In 2017, the same group developed a cobalt (III) catalytic system for the addition of aromatics and heteroaromatics to 1,1-disubstituted allenes.[147] These conditions yielded the corresponding alkenylated compounds due to an isomerization and a protonation step (Scheme 83).

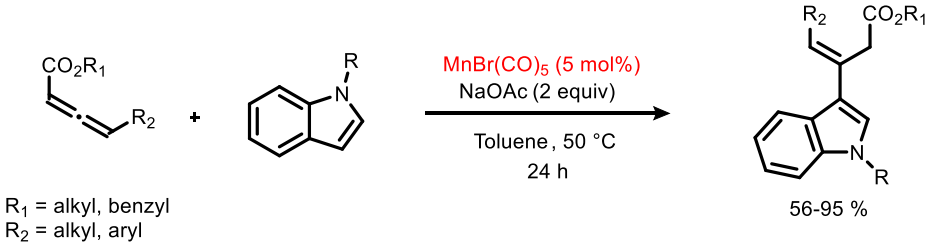


Scheme 83 : cobalt-catalyzed alkenylation of indoles.

- Manganese

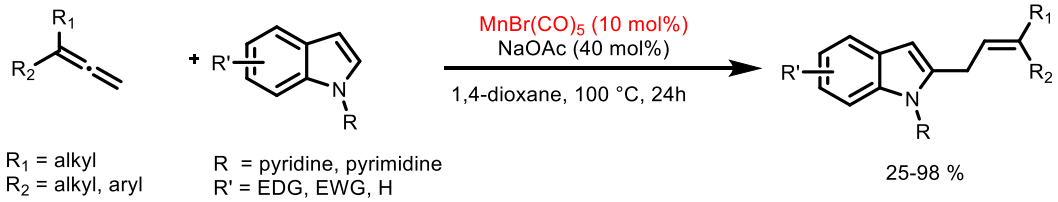
[145] C. Ghosh, P. J. Nagtilak, M. Kapur, *Org. Lett*. **2019**, 21, 3237.
[146] S. Nakanowatari, L. Ackermann, *Chem. Eur. J.* **2015**, 21, 16246.
[147] S. Nakanowatari, R. Mei, M. feldt, L. Ackermann, *ACS Catal*. **2017**, 7, 2511.

Manganese has been also employed in this reaction by Rueping's group.[148] Using catalytic amount of $MnBr(CO)_5$, they realized the addition of indoles derivatives to 1,3-disubstituted allenes, giving access to alkenyl products through the indole insertion on the central carbon (Scheme 84).



Scheme 84 : hydroalkenylation of indoles by manganese based catalytic system.

Using the same manganese salt, Wang and coworkers reported the hydroarylation of 1,1-disubstituted allenes.[149] Under inert atmosphere and in presence of catalytic amount of sodium acetate, the allylation of (hetero)-aromatics was carried out at 100 °C to afford the linear product in moderate to excellent yields (Scheme 85).

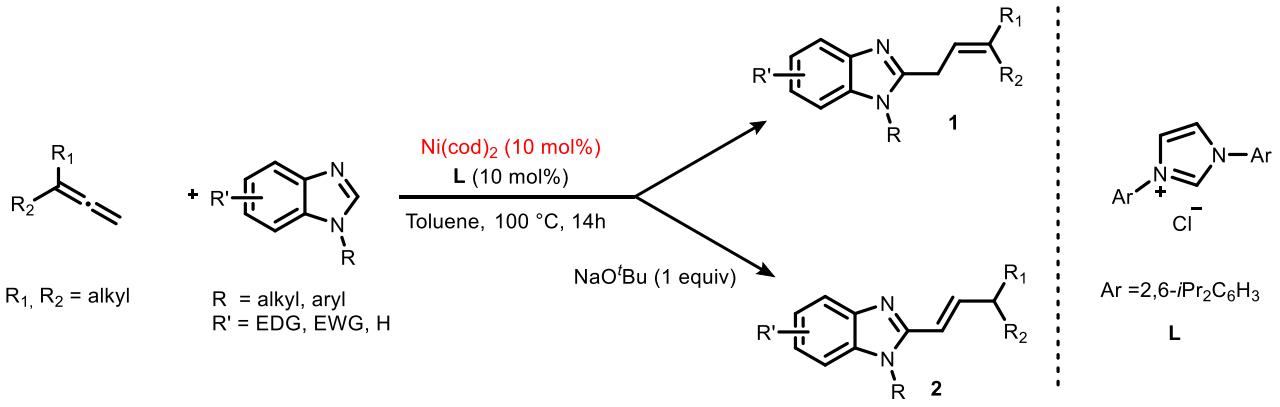


Scheme 85 : manganese-catalyzed hydroarylation of 1,1-disubstituted allenes

- Nickel

In 2017, Ackermann reported the allylation and the alkenylation of imidazole and purine derivatives by using $Ni(cod)_2$ as catalyst and a NHC ligand.[150] The authors showed a base effect: the reaction with 1,1-disubstituted allenes affords selectively the allylic product **1**, while in presence of sodium *tert*-butoxide this product undergoes an isomerization to yield only the corresponding vinyl product **2** (Scheme 86).

[148] C. Wang, A. wang, M. Rueping, *Angew. Chem. Int. Ed*, **2017**, 56, 1.
[149] S.-Y. Chen, Q. Li, H. Wang, *J. Org. Chem.* **2017**, 82, 11173.
[150] S. Nakanowatari, T. Müller, J. C. A. Oliveira, L. Ackermann, *Angew. Chem. Int. Ed*. **2017**, 56, 15891.

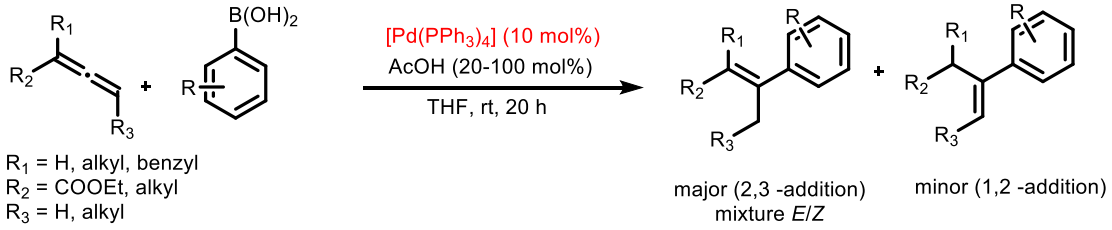


Scheme 86 : nickel-catalyzed allylation and alkenylation of imidazole and purine.

b. Boronic acid addition

Organoboronic acid acting as nucleophile have been employed as an important alternative for the hydroarylation of allene to create new C-C bonds. Despite the fact that this reaction produces boronic byproducts, it can offer an interesting alternative for the C-H functionalization methodology.

Palladium was the first metal involved in this reaction. By using 10 mol% of palladium salt, Ma's group reported the first regio- and stereoselective addition of phenylboronic acid to mono-, di- and tri-substituted allenes, in presence of acetic acid (Scheme 87).[151] The main drawback of this method is the selectivity of the addition. Depending on the steric hindrance of the allene substituents the reaction occurs by 1,2- or 2,3-addition, affording thus two different regioisomers. Later they extended this reaction to 1,2-allenic phosphonates [152], sulfones and sulfoxides.[153]

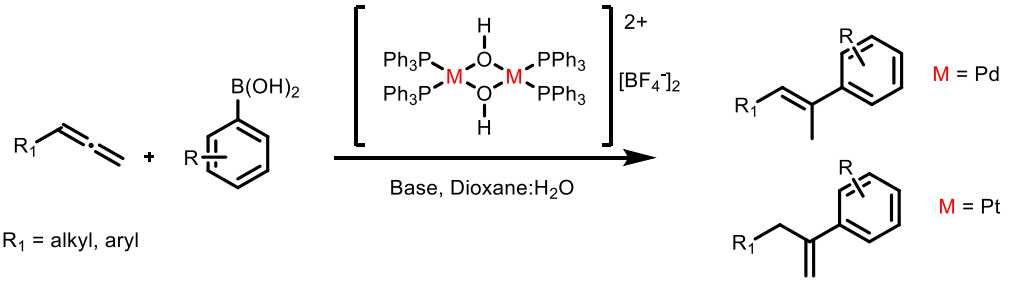


Scheme 87 : addition of aryl boronic acid to 1,1-disubstituted using palladium based catalytic system.

Oh's group also published the addition of different boronic acid to mono and di-substituted allenes by using 3 mol% of $[Pd(PPh_3)_4]$ and 10 mol% of acetic acid.[154] The addition of an electron rich phenyl boronic acid was selective with mono and 1,1-disubstituted allenes, whereas with 1,3-disubstituted allenes a mixture of *E* and *Z* isomers were obtained with low selectivity (a ratio 1: 1).

Depending on the metal, Yoshida and co-workers controlled the regioselectivity of the arylboronic acid addition.[155] The endo-olefinic product was formed when they used hydroxopalladium complex, while the reaction with hydroxoplatinium complex yield the exo-olefinic compound (Scheme 88).

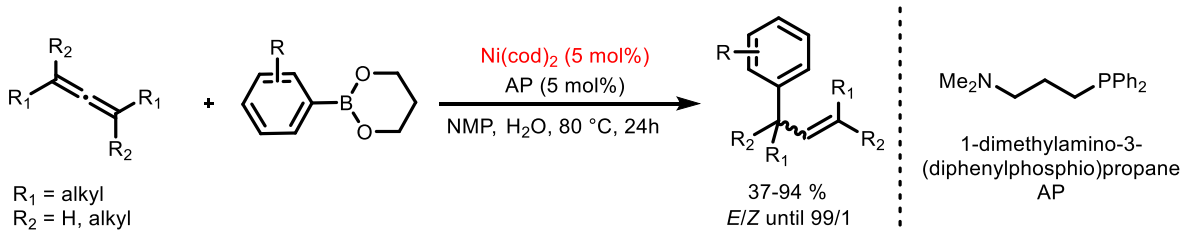
[151] S. Ma, N. Jiao, L. Ye, *Chem. Eur. J.* **2003**, 9, 6049.
[152] S. Ma, H. Guo, F. Yu, *J. Org. Chem*. **2006**, 71, 6634
[153] H. Guo, S. Ma, *Synthesis*. **2007**, 17, 2731.
[154] C. H. Oh, T. W. Ahn, R. Reddy, *Chem. Commun*., **2003**, 2622.
[155] M. Yoshida, K. Matsuda, Y. Shoji, T. Gotou, M. Ihara, K. Shishido, *Org. Lett.* **2008**, 10, 5183.



Scheme 88 : regiocontrolled addition of aryl boronic acid.

Associated to sodium hydroxide, $PdCl_2$ was used as catalyst for the addition of arylboronic acids to diphenylphosphorylallenes.[156] This family of allene has been tested also with a rhodium catalytic system.[157]

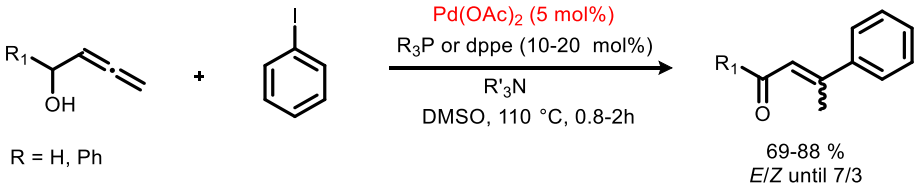
Nickel was also used as catalyst for the addition of arylboronates to allenes. The reaction is carried out at 80 °C with 5 mol% of $Ni(cod)_2$ and 5 mol% of 1-dimethylamino-3-(diphenylphosphio)propane (AP) as P,N-ligand.[158] The addition of the aryl occurs selectively on the external carbon of the di- or tetra-substituted allene (Scheme 89). A mixture of *E* and *Z* isomers was obtained in most of the cases.



Scheme 89 : nickel-catalyzed addition of arylboronate on allenes.

c. Other ways

In 1985, Tsuji reported a palladium-based catalytic system for the addition of aryl halide on allene.[159] The reaction between 2,3-butadien-1-ol and iodobenzene was carried out in presence of 5 mol% of $Pd(OAc)_2$ and catalytic amount of phosphine ligand, to afford at 110 °C the regioselective addition of the benzene moiety on the central carbon (Scheme 90). This method presents a poor stereoselectivity giving a mixture of *E* and *Z* of the α,β-unsaturated carbonyl.



Scheme 90 : palladium-catalyzed arylation with iodobenzene.

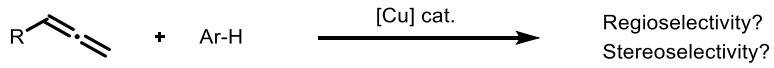
Larock and coworkers developed similar conditions for the allenes hydroarylation with aryl iodide derivatives, followed by carboannulation or heteroannulation.[160]

[156] Y. Chen, D.-M. Ma, F.-F. Ba, J. Sun, T. Liu, L. Zhu, M.-D. Zhoua, *Adv. Synth. Catal.* **2016**, 358, 2849.
[157] T. Nishimura, S. Hirabayashi, Y. Yasuhara, T. Hayashi, *J. Am. Chem. Soc.* **2006**, 128, 2556.
[158] G. Takahashi, E. Shirakawa, T. Tsuchimoto, Y. Kawakami, *Adv. Synth. Catal.* **2006**, 348, 837.
[159] I. Shimizu, T. Sugiura, J. Tsuji, *J. Org. Chem*. **1985**, 50, 537.
[160] a) R. Larock, J. Zenner, *J. Org. Chem*. **1995**, 60, 482. b) R. Larock, N. Berrious-Pena, C. Fried, *J. Org. Chem*. **1991**, 56, 2615.

Allene hydroarylation is extremely restricted to electron-rich arenes and heteroaromatics. This type of functionalization requires an active catalyst. In this chapter, we report a direct allene hydroarylation realized by copper catalyzed system with a total atom economy.

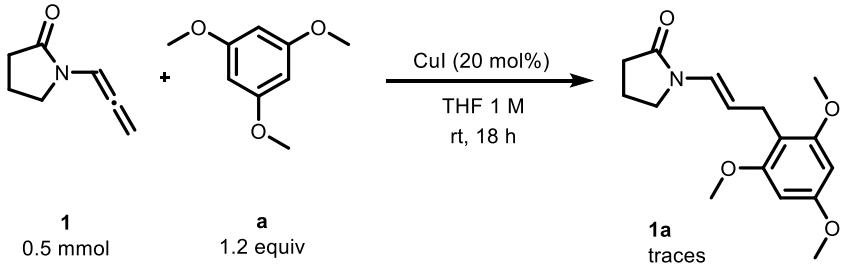
2. Results and discussion

Recently, we get interested in a direct hydroarylation of allenes catalyzed by copper to create new C-C bond and to study the regio- and the stereoselectivity of this reaction (Scheme 91).



Scheme 91 : the objective of this study.

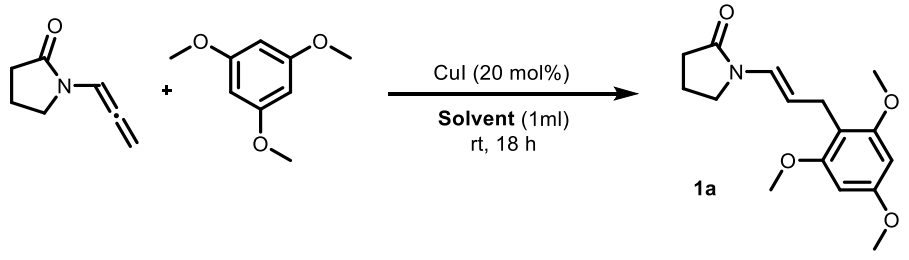
Based on all the previous allene hydrofunctionalization developed in our group, we started with *N*-allenyl-2-pyrrolidinone **1** as allene model to develop the hydroarylation system. Build on what is existing in the literature, we chose 1,3,5-trimethoxybenzene **a** as best candidate for two main reasons: it is an electron rich aryl and it bears oxygen atoms as directing group. We realized our first attempt in 0.5 ml THF at room temperature by using 20 mol% of copper iodide (Scheme 92). After 18h, traces of the *E*-allylic product **1a** were detected by GC-MS analysis.



Scheme 92 : initial attempt.

We realized that a dilution was necessary to increase the solubility of the 1,3,5-trimethoxybenzene. So, we used 1 ml of THF to work in a concentration of 0.5 M instead of 1 M. With this dilution, the desired product was formed in 10% of yield. We realized this reaction in different solvents to check their influence (Table 14). In dioxane, the reaction did not afford the hydroarylated product and the starting materials are completely recovered at the end (Entry 2). DMF was able to promote this addition, and yields **1a** in 17 % (Entry 3). While acetonitrile showed to be the efficient one: the product **1a** was formed with 23 % of yield (Entry 4). Using acetonitrile as best solvent, we realized a blank test to verify the necessity of the copper for this reaction. The absence of copper leads to a complete loss of reactivity without any conversion of the starting materials (Entry 5).

Table 14 : solvent effect on the formation of **1a**.

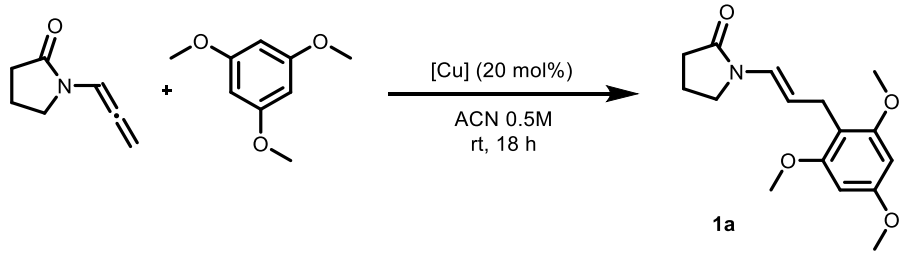


Entry	Solvent	Yield % [a]
1	THF	10
2	1,4-dioxane	0
3	DMF	17
4	ACN	23
5[b]	ACN	0

Reaction carried out with 0.5 mmol of allene **1**, 0.6 mmol of 1,3,5-trimethoxybenzene **a**, 0.1 mmol of CuI in 1 ml of solvent under an inert atmosphere, stirred at 30 °C for 18 hours. [a]Yield evaluated by ^{1}H NMR with 4-iodoanisole as internal standard. [b] reaction without CuI.

Therefore, we proved that copper is necessary for this reaction. We then started to test different copper sources. A serie of copper salts have been engaged in the reaction conditions (Table 15). The replacement of copper iodide by copper bromide did not improve the yield (Entry 2). While, copper tetrakis acetonitrile showed a good activity and afforded the hydroarylated product **1a** with good yields (Entries 3 and 4, respectively 51 and 47 %). Copper acetate was less suitable for this functionalization and gave a poor yield (Entry 5, 13 %). With 20 mol% of copper (I) trifluoromethanesulfonate benzene complex, **1a** was formed with very good yield (Entry 6, 78%). We were interested by this good result, but it was necessary to explain if the high reactivity with $(CuOTf)_2$.benzene is due to the copper's counter ion or if it is simply due to the quantity of copper which is 40 mol% in the reality. So, we did a test with 20 mol% of $Cu(OTf)_2$, the yield was 16% (Entry 7) excluding the importance of the counterion. Another test with 10 mol% of $(CuOTf)_2$.benzene has been achieved (Entry 8). The yield decreased to 41% referring the previous good result (Entry 6) to the copper quantity. We decide to use $Cu(CH_3CN)_4PF_6$ as it gave the best yield.

Table 15 : tests with different copper salts.



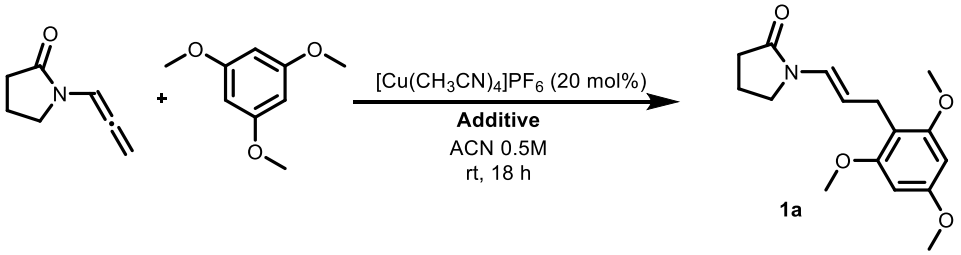
Entry	[Cu]	Yield % [a]
1	CuI	23
2	CuBr	21
3	$Cu(CH_3CN)_4PF_6$	51
4	$Cu(CH_3CN)_4BF_4$	47
5	CuOAc	13
6	$(CuOTf)_2$.benzene	78
7	$Cu(OTf)_2$	16
8	$(CuOTf)_2$.benzene[b]	41

Reaction carried out with 0.5 mmol of allene **1**, 0.6 mmol of 1,3,5-trimethoxybenzene **a**, 0.1 mmol of Copper salt in 1 ml of ACN under an inert atmosphere, stirred at 30 °C for 18 hours. [a]Yield evaluated by ^{1}H NMR with 4-iodoanisole as internal standard. [b]10 mol% of copper salt.

In order to improve the yield, we tried to add a ligand to see if the activity of the catalytic system can increase (Table 16). With 20 mol % of triphenylphosphine the yield was almost the same (Entry 2). When we used 40 mol% of this ligand the reactivity decreased and we obtained only 19% of **1a** (Entry

3). We changed the type of the ligand and we used the bidentate phenanthroline. With 20 mol% of the latter one, only traces of the product were formed (Entry 4). In order to find another solution, we then began to test several cocatalysts to see their effects. Based on the cocatalysts already used for the allene hydroarylation with different metals such as gold, we realized different tests. Using 20 mol% of TFA, the desired reaction did not occur and the allenamide was completely decomposed after 18h of reaction (Entry 5). While adding 20 mol% of silver triflate, acetate or sodium acetate did not show any positive effect, and did not give any additional efficiency to the system. Thus, **1a** was formed with almost similar yields (Entries 6-8). These tests showed no positive effect of ligand and additive, so we kept the additive-free system.

Table 16 : ligand and addditives effects on the reaction.

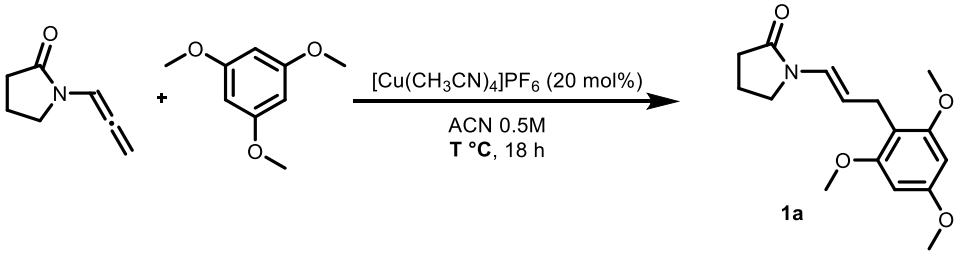


Entry	Additive	Yield %[a]
1	-	51
2	PPh_3 (20 mol%)	48
3	PPh_3 (40 mol%)	19
4	Phenantroline (20 mol%)	traces
5	TFA (20 mol%)	0
6	AgOAc (20 mol%)	51
7	AgOTf (20 mol%)	50
8	NaOAc (20 mol%)	48

Reaction carried out with 0.5 mmol of allene **1**, 0.6 mmol of 1,3,5-trimethoxybenzene **a**, 0.1 mmol of $Cu(CH_3CN)_4PF_6$ and x mmol of additive in 1 ml of ACN under an inert atmosphere, stirred at 30 °C for 18 hours. [a] Yield evaluated by ^1H NMR with 4-iodooanisole as internal standard.

The following tested parameter was the temperature. We started by slightly increasing the temperature to check its influence (Table 17). At 40 °C the yield was almost the same with the one at 30 °C (Entries 1-2, 54 and 51% respectively). When we reached the boiling point of the acetonitrile, we got **1a** in good yield 76% (Entry 3). Therefore, increasing temperature has a beneficial effect. When the reaction is carried out at 100 °C, the allene is totally converted and the hydroarylated product was formed in 90% of yield (Entry 4).

Table 17 : temperature effect on the reaction.

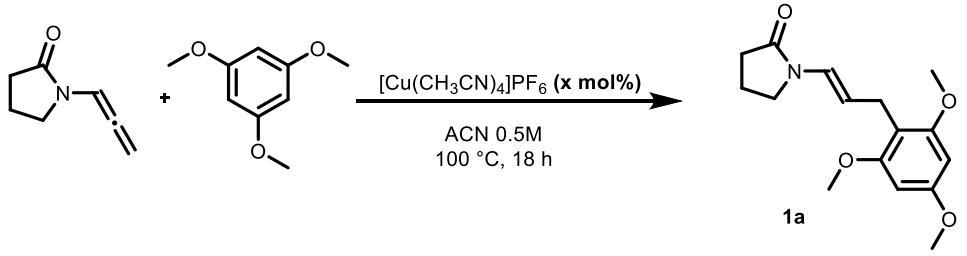


Entry	T °C	Yield %[a]
1	30	51
2	40	54
3	82	76
4	100	90

Reaction carried out with 0.5 mmol of allene **1**, 0.6 mmol of 1,3,5-trimethoxybenzene **a**, 0.1 mmol of $Cu(CH_3CN)_4PF_6$ in 1 ml of ACN under an inert atmosphere, stirred at T °C for 18 hours. [a] Yield evaluated by ^1H NMR with 4-iodoanisole as internal standard.

Encouraged by this excellent result, we were looking to decrease the catalytic charge (Table 18). Reducing the quantity of $Cu(CH_3CN)_4PF_6$ from 20 to 15 mol% did not affect the reactivity, and **1a** was formed in 90 % (Entry 2). Even when we used just 10 mol% of copper, the obtained yield was very good 88%, proving the efficiency of this system (Entry 3). Whereas, 5 mol% of copper were not enough and gave **1a** in 49% of yield (Entry 4). Based on these results, we followed the study with 10 mol% of $Cu(CH_3CN)_4PF_6$.

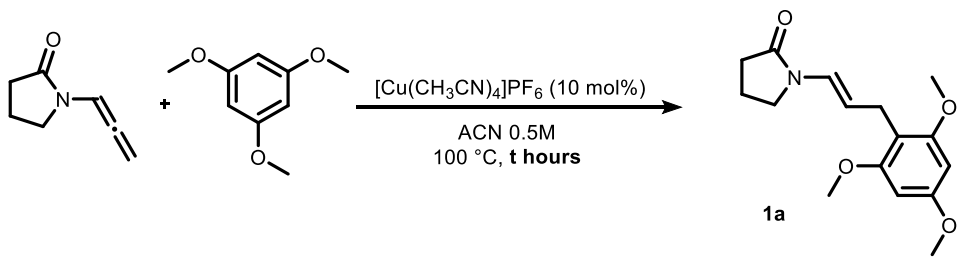
Table 18 : decreasing the catalytic charge and its effect on the reaction.

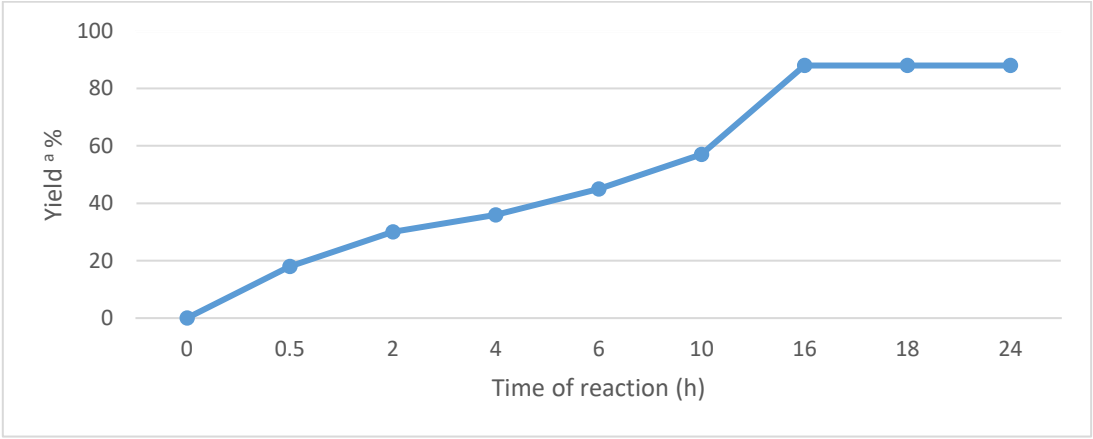


Entry	x mol%	Yield %[a]
1	20	90
2	15	90
3	10	88
4	5	49

Reaction carried out with 0.5 mmol of allene **1**, 0.6 mmol of 1,3,5-trimethoxybenzene **a**, x mmol of $Cu(CH_3CN)_4PF_6$ in 1 ml of ACN under an inert atmosphere, stirred at 100 °C for 18 hours. [a] Yield evaluated by ^1H NMR with 4-iodoanisole as internal standard.

These parametric studies have been followed by a kinetic study to control the reaction evolution and the formation of **1a** (Figure 22). We realized that the reaction rate in the beginning is slightly high and the yield reach 36% in 2 h. Then, this rate decreases. Thus, after 16 hours at 100 °C the yield reached its maximum with 88%.

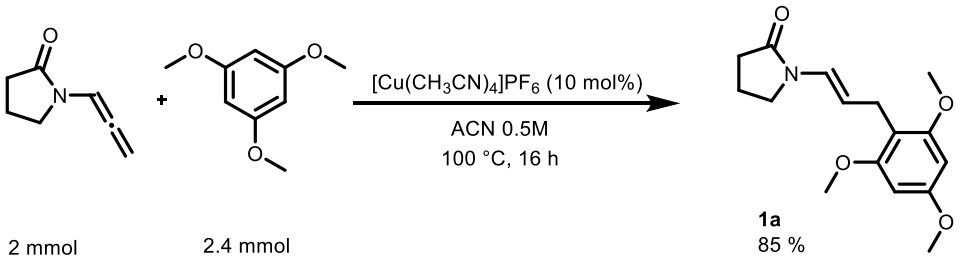




Reaction carried out with 0.5 mmol of allene **1**, 0.6 mmol of 1,3,5-trimethoxybenzene **a**, 0.05 mmol of $Cu(CH_3CN)_4PF_6$ in 1 ml of ACN under an inert atmosphere, stirred at 100 °C for x hours. [a] Yield evaluated by ^1H NMR with 4-iodoanisole as internal standard.

Figure 23 : kinetic evolution of the reaction.

After the reaction optimisation, we fixed the method conditions. First, we applied this method on 2 mmol of allene to check its application on a bigger scale. **1a** was formed selectively with a yield of 85%, proving the efficiency of this reaction on a large-scale (Scheme 93).

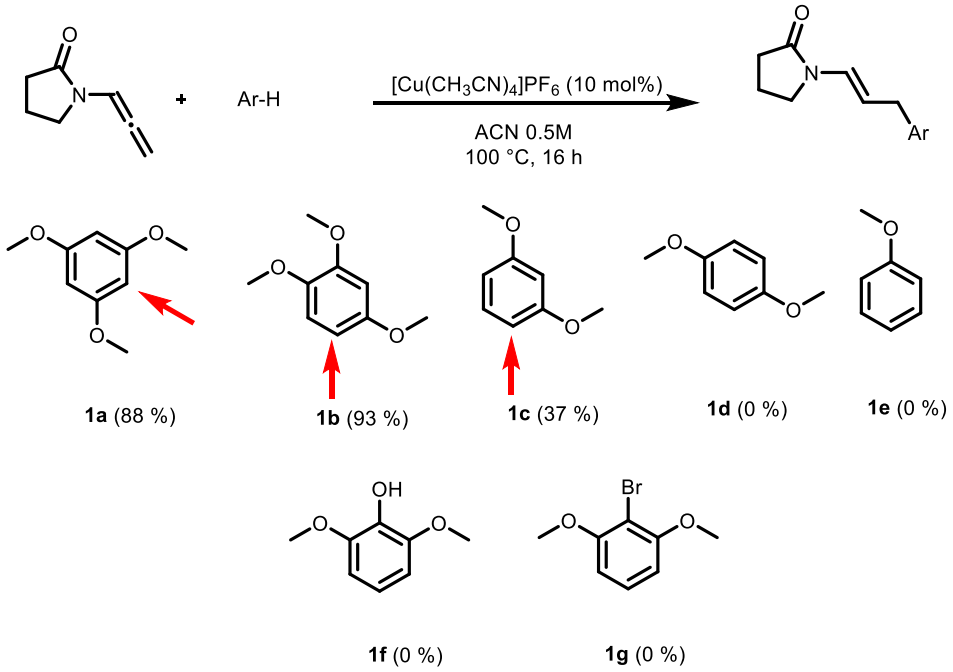


Scheme 93 : hydroarylation in large scale.

Based on these tested parameters, we started to extend this original reactivity on different aromatics and hetero-aromatics combined with various allenes.

3. Scope and limitations

The reaction optimization was realized with 1,3,5-trimethoxybenzene. So we began the study of the method's extension with similar electron rich aromatics containing at least one oxygen atom as directing group (Scheme 94). The reaction with 1,2,4-trimethoxybenzene affords the product **1b** with excellent yield (93 %). While, when the aromatic is substituted by just 2 methoxy groups the reactivity decreased and we obtained 37% with 1,3-dimethoxybenzene **1c**, and 0 % in the case of 1,4-dimethoxybenzene **1d**. The reaction of the allene with anisole did not afford the desired product **1e** and the allene was totally recovered maybe because anisole is not so much electron rich. To check the effect of some substituents on the electron rich arenes we applied the reaction conditions on 2,6-dimethoxyphenol and 2-bromo-1,3-dimethoxybenzene. Both of the aromatics showed to be unsuitable partners for this reaction (0% for **1f** and **1g**).



Scheme 94 : hydroarylation with electron-rich aryls.

Taking on consideration the electronic effect of the aromatics tested and cited above, we were wondering about the oxygen effect in those molecules. So, we decided to test the reactivity of mesitylene, an electron rich aromatic which is not bearing any heteroatom (Figure 24). The reaction did not yield any traces of product **1h**. Another test has been realized with toluene, and it failed as well (**1i**). To be sure, from the unreactivity of the last one, we made a test in toluene as reagent and solvent in the same time. The result was the same and we only recovered the starting materials.

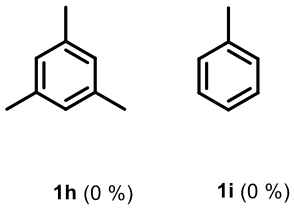


Figure 24 : electron rich aryls without heteroatoms.

Based on these results, we deduced the importance of the heteroatom presence so we started to engage heteroaromatics in this reaction (Figure 25). The reaction with *N*-methylindole gave the desired product with good yield (77% for **1j**). 2-methyl- and 2-phenylpyridine failed to add to allenamide (0 % for **1k** and **1l**). We supposed that the copper activity in both cases is lost due to a possible coordination of the metal to the nitrogen atom. The reaction with benzofuran affords the hydroarylated product **1m** with 41% of yield. While, 2,5-dimethylfuran and benzothiophene are not reactive and the reaction did not afford the desired products **1n** and **1o**. On the other hand, 3-methoxythiophene and 3,4-dimethoxyhiophene showed to be very reactive, thus yielding the corresponding coupled product with good to excellent yield (76 and 91% respectively for **1p** and **1q**). Using *N*-phenyl pyrrole, only 15 % of the product **1r** were formed. Whereas, 1-phenylpyrrolidine-2,5-dione did not react with the allene in our conditions (0 % for **1s**).

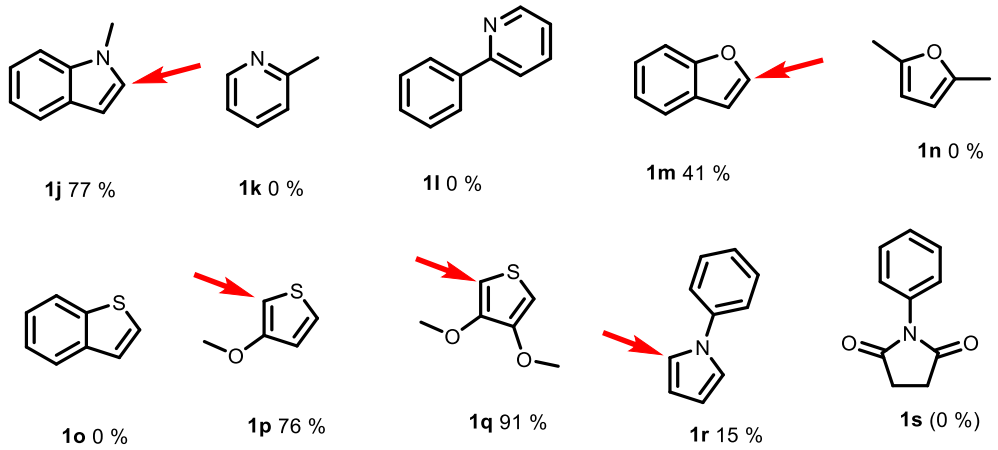


Figure 25 : hydroarylation with heteroaromatics.

We also tested another type of aryl substituted by directing groups to check the influence of the last one (Figure 26). In the case of *N*-methoxybenzamide, 27 % of the product **1t** was formed with total consumption of the starting aryl. On the other hand, the reaction of *N*-phenylacetamide with the allene did not afford the desired product **1u**.

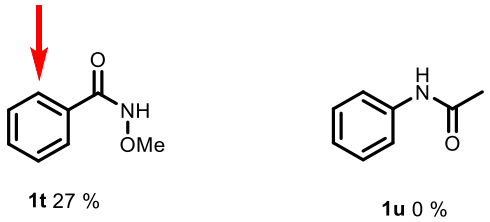


Figure 26 : hydroarylation with benzamide and anilide.

We were not surprised by the reactivity of the (hetero)-aromatics, and we expected this limitation on the aryl's scope. This limitation may refer to the necessity of a highly electron rich aryl, and the presence of an heteroatom.

Then, we explored the reactivity of allenes in the same conditions. We tested different allenes with 1,3,5-trimethoxybenzene.

The reaction of cyclohexylallene with trimethoxybenzene was unsuccesfull and we recovered around 70 % of cyclohexylallene, without the formation of a new product. The lost quantity might be due to a decomposition. When we applied this reaction on methoxyallene, traces of **3a** were formed. We had set up both of these reactions at the allenes's corresponding boiling point (respectively at 55 and 50 °C) to avoid their decomposition under thermal conditions (Figure 27).

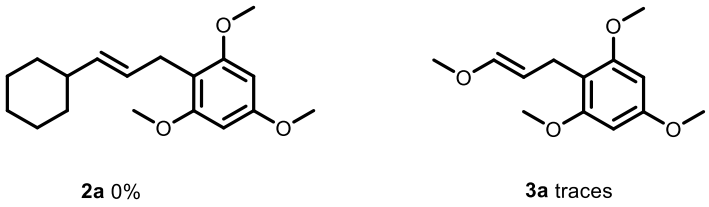


Figure 27 : hydroarylation of alkyl- and alkoxy-allene.

We also applied the reaction conditions on allenyl phosphonate to see if the presence of phosphonate group can influence the hydroarylation or can control the selectivity. When we engaged

diethyl propa-1,2-dien-1-ylphosphonate in the reaction, we did not detect any new product (Figure 28).

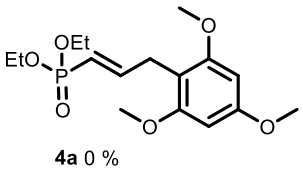


Figure 28 : hydroarylation of allenyl phosphonate.

We then decided to investigate the copper catalyzed hydroarylation on a family of allenamide and allenyl sulfonamide (Figure 29). The *N*-allenyl-oxazolidinone reacts with 1,3,5-trimethoxybenzene and affords the product **5a** with good yield (71%). Another cyclic allenamide was tested : *N*-allenyl-2-valerolactam. We were surprised by the lack of reactivity with this allene which gave only 14% of **6a**. Allenyl sulfonamide gave corresponding hydoarylated products with good yields (61 and 64% respectively for **7a** and **8a**).

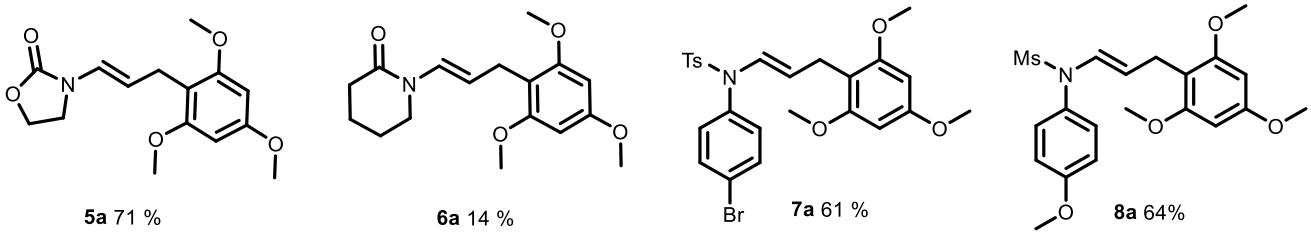


Figure 29 : hydroarylation of allenamide and allene sulfonamide.

At the moment of writing this chapter, the scope of allene is not finished yet. Several allenamide and allenyl sulfonamide will be tested in the application of this reaction.

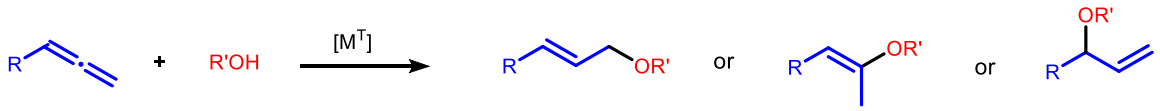
4. Conclusion

To conclude, we developed a simple system for the hydroarylation of *N*-allenamides and *N*-sulfonamides by using a cheap and abundant metal as catalyst. This intermolecular reaction is developed with total regio- and stereoselectivity to afford the (*E*)-allylic product. This ligand-free method give the desired product with a total atom economy.

Interesting by the direct hydroarylation, without using an intermediate like boronic acid, we are planning to study its mechanism.

III. Intermolecular hydroalkoxylation of allenes

The hydroalkoxylation of allenes is less described than the hydroarylation. This method aims to create new C-O bond for the synthesis of vinylic or allylic ethers (Scheme 95). This reaction was performed with aliphatic alcohols and rarely with phenol derivatives. Three principal metals have been used to catalyse this reaction: palladium, gold and rhodium.

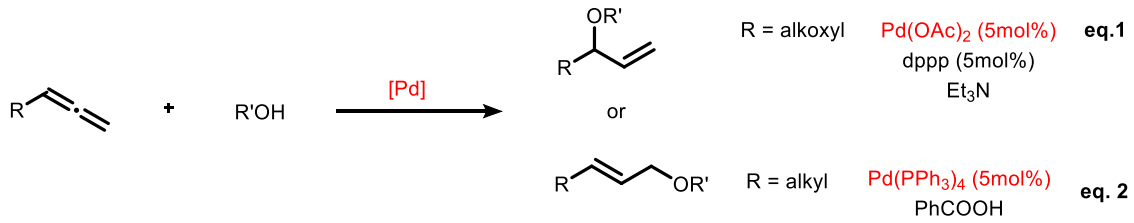


Scheme 95 : metal transition-catalyzed hydroalkoxylation.

1. State of the art

Allene hydroalkoxylation have been studied for the first time by Rutjes in 1998, by using palladium-based catalytic system (Scheme 96, eq. 1).[161] The reaction of alcohols with alkoxyallene affords exclusively the branched product by the alcohol insertion on the carbon atom bearing the alkoxy group. Using different palladium catalytic system, many reports published later proved this regioselectivity when it concerns the functionalization of alkoxyallenes.

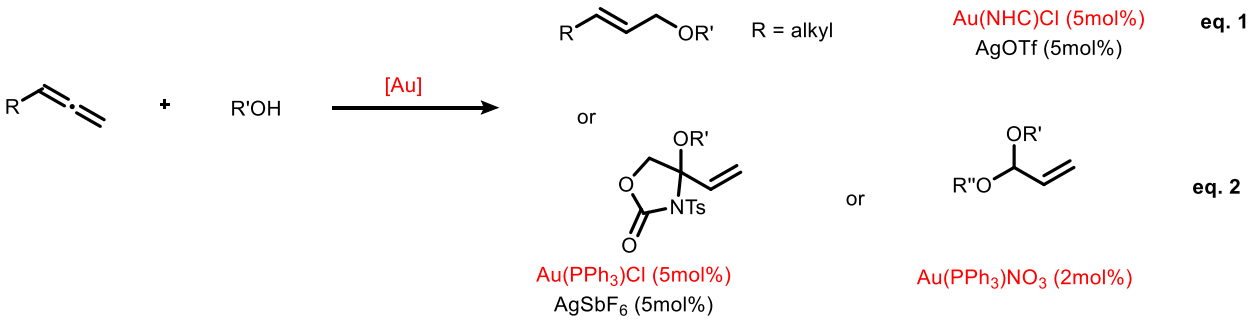
Yamamoto and coworkers synthesized selectively the allylic ether when they realized the hydroakoxylation of alkylallene, showing thus the electronic effect on the regioselectivity (Scheme 96, eq. 2).[162]



Scheme 96 : palladium-catalyzed hdroalkoxylation of allenes.

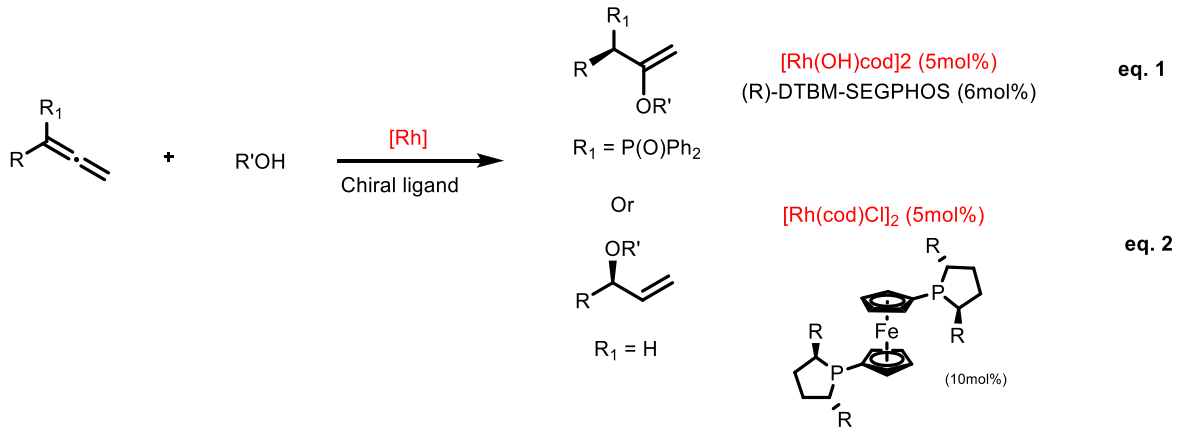
Gold was the most used transition metal to catalyse the hydroalkoxylation of allenes. In 2008, Widenhoefer developed the first regio- and stereoselective synthesis of allylic ether catalyzed by gold (Scheme 97, eq. 1).[163] Later, different groups reported a gold catalytic system for the intermolecular hydroalkoxylation to afford the linear product.[164] Few examples showed another regioselectivity like Tamaru's[165] and Zhang's[166] reports when they worked respectively on 4-vinyldiene-2-oxazolidinone and alkoxyallene (Scheme 97, eq. 2).

[161] F. P. J. T. Rutjes, T. M. Kooistra, H. Hiemstra, H. E. Schoemaker, *Synlett*, **1998**, 192.
[162] N. T. Patil, N. K. Pahadi, Y. Yamamoto, *Can. J. Chem.,* **2005**, 83, 569.
[163] Z. Zhang, R. A. Widenhoefer, *Org. Lett.*, **2008**, 10, 2079.
[164] Some examples : a) S. Webster, D. R. Sutherland, A. –L. Lee, *Chem. Eur. J.* **2016**, 22, 18593. b) R. S. Paton, F. Maseras, *Org. Lett.* **2009,** 11, 2237.
[165] Y. Horino, Y. Takata, K. Hashimoto, S. Kuroda, M. Kimura, Y. Tamaru, *Org. Biomol. Chem.*, **2008**, 6, 4105.
[166] D.-M. Cui, Z. –L. Zheng, C. Zhang, *J. Org. Chem.*, **2009**, 74, 1426.



Scheme 97 : gold-catalyzed hdroalkoxylation of allenes.

Compares to gold, rhodium has been used timidly in the hydroalkoxylation. In 2009, Hayashi's group reported a rhodium based catalytic system for the hydroalkoxylation of diphenylphosphine allene.[167] Due to the allene nature, the addition of the alkoxy moiety occured selectively on the central carbon. A chiral diphosphine ligand have been used to control the reaction enantioselectivity (Scheme 98, eq. 1). While in 2016, Breit and coworkers performed a regio and enantioselective hydroalkoxylation on allene alkyl[168]. This method afforded the corresponding branched product with good selectivities (Scheme 98, eq. 2).



Scheme 98 : rhodium-catalyzed hdroalkoxylation of allenes.

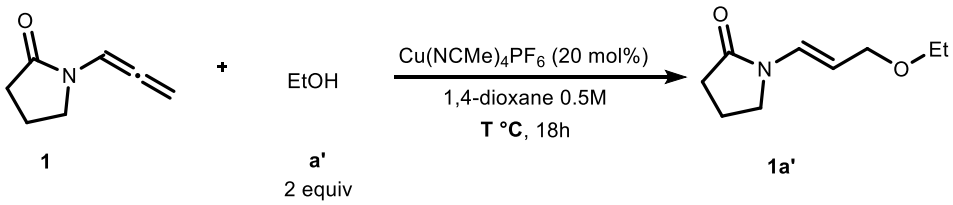
In this part, we aimed to realize the hydroalkoxylation of allenamide to afford a serie of allylic ethers by using a simple copper catalytic system.

2. Preliminary tests

Based on previous works, we began our preliminary tests with *N*-allenyl-pyrrolidinone and ethanol as model substrates to develop suitable reaction conditions. With 20 mol% of $Cu(CH_3CN)_4PF_6$, we used 2 equiv of ethanol in 1ml of 1,4-dioxane (Table 19). When we carried out the reaction at 30 °C, the corresponding allylic ether **1a'** was obtained with a very low yield (Entry 1, 10%). Increasing the temperature has influenced slightly the yield of **1a'**, affording 18% and 21% respectively at 50 and 75 °C (Entries 2-3).

[167] T. kawaamoto, S. Hirabayashi, X. –X. Guo, T. Nishimura, T. Hayashi, *Chem. Commun.*, **2009**, 3528.
[168] Z. Liu, B. Breit, *Angew. Chem. Int. Ed.* **2016**, 55, 8440.

Table 19 : temperature effect on the formation of **1a'**.

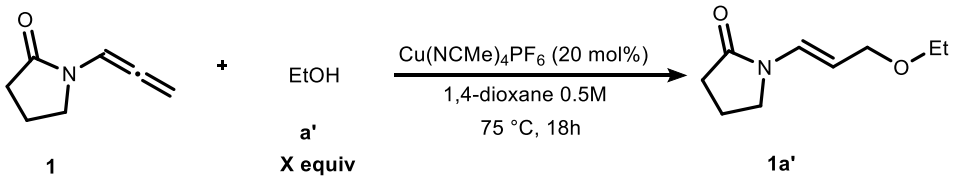


Entry	T °C	Yield %[a]
1	30	10
2	50	18
3	75	21

Reaction carried out with 0.5 mmol of allene, 1 mmol of ethanol, 0.1 mmol of copper salt in 1 ml of 1,4-dioxane under an inert atmosphere, stirred at T °C for 18 hours. [a]Yield evaluated by ^{1}H NMR with 1,3,5-trimethoxybenzene as internal standard.

In order not to exceed the ethanol boiling point, the higher temperature that we reached was 75 °C (Table 20). The reaction with 3, 4, and 5 equiv of ethanol did not improve the yield (Entries 2-4). While using 10 equiv of ethanol affords the allylic ether **1a'** with 51% of yield (Entry 5). Encouraged by this result, and to check if it is an equivalence limitation we set up this reaction in ethanol as solvent and reagent in the same time. In 1 ml of ethanol which is around 34 equiv, **1a'** was formed in good yield (Entry 6, 81%). Trying to decrease ethanol equivalence, we repeated this reaction in 0.5 and 0.2 ml of ethanol, the reactivity was very low to null (Entries7-8). It may be due to the solubility effect. Using 1 ml of freshly distilled ethanol, the allylic product was formed with 87% of yield (Entry 9).

Table 20 : tests with different amounts of ethanol.



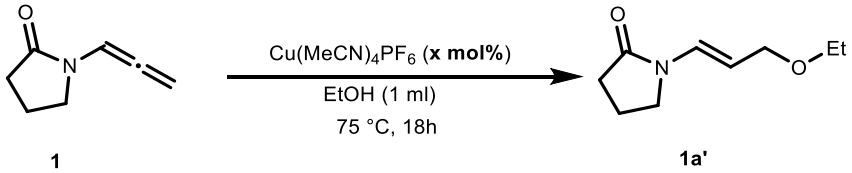
Entry	X equiv	Yield %[a]
1	2	21
2	3	21
3	4	22
4	5	24
5	10	51
6	34 (1ml) [b]	81
7	17 (0.5ml) [b]	15
8	7 (0.2ml) [b]	0
9	33 (1ml)[b,c]	87

Reaction carried out with 0.5 mmol of allene, x mmol of ethanol, 0.1 mmol of copper salt in 1 ml of 1,4-dioxane under an inert atmosphere, stirred at 75 °C for 18 hours. [a] Yield evaluated by ^{1}H NMR with 1,3,5-trimethoxybenzene as internal standard. [b] reaction carried out in the indicated volume of ethanol. [c] Ethanol is freshly distilled.

Then, we realized a blank test to check the necessity of the copper for this hydroalkoxylation (Table 21). In absence of copper, the allene did not react and it was completly recovered after 18h

(Entry 2). This test proved the importance of copper for this reaction. With the good yield obtained in ethanol as reagent-solvent, we decided to decrease the copper charge. In presence of 15 mol% of copper, **1a'** was formed with 83 % (Entry 3). A good yield was obtained also with 10 mol% of $Cu(CH_3CN)_4PF_6$ (Entry 4, 78%). Therefore, we continued the conditions optimization with 10 mol% of copper salts.

Table 21 : effect of the copper charge on the formation of **1a'**.

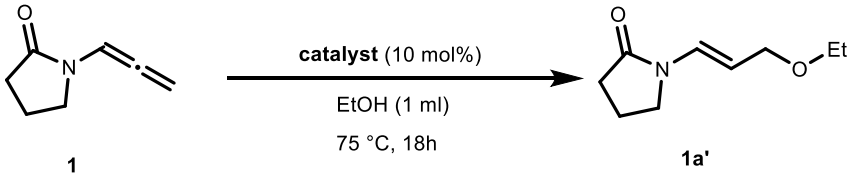


Entry	X mol %	Yield %[a]
1	20	87
2	0	0
3	15	83
4	10	78

Reaction carried out with 0.5 mmol of allene, x mol % of copper salt in 1 ml of ethanol under an inert atmosphere, stirred at 75 °C for 18 hours. [a] Yield evaluated by ^{1}H NMR with 1,3,5-trimethoxybenzene as internal standard.

We tested then the reactivty of many copper catalysts in this reaction (Table 22). $Cu(CH_3CN)_4BF_4$ had apparently the same catalytic effect of $Cu(CH_3CN)_4PF_6$ yielding the desired product with 77% (Entry 2). Using copper acetate as catalyst, **1a'** was formed only in 18% (Entry 3). While in presence of CuCN, CuTc and CuBr the addition of the alcohol on the allene failed, and the allene was not converted (Entries 4-6).

Table 22 : tests with different copper salts.

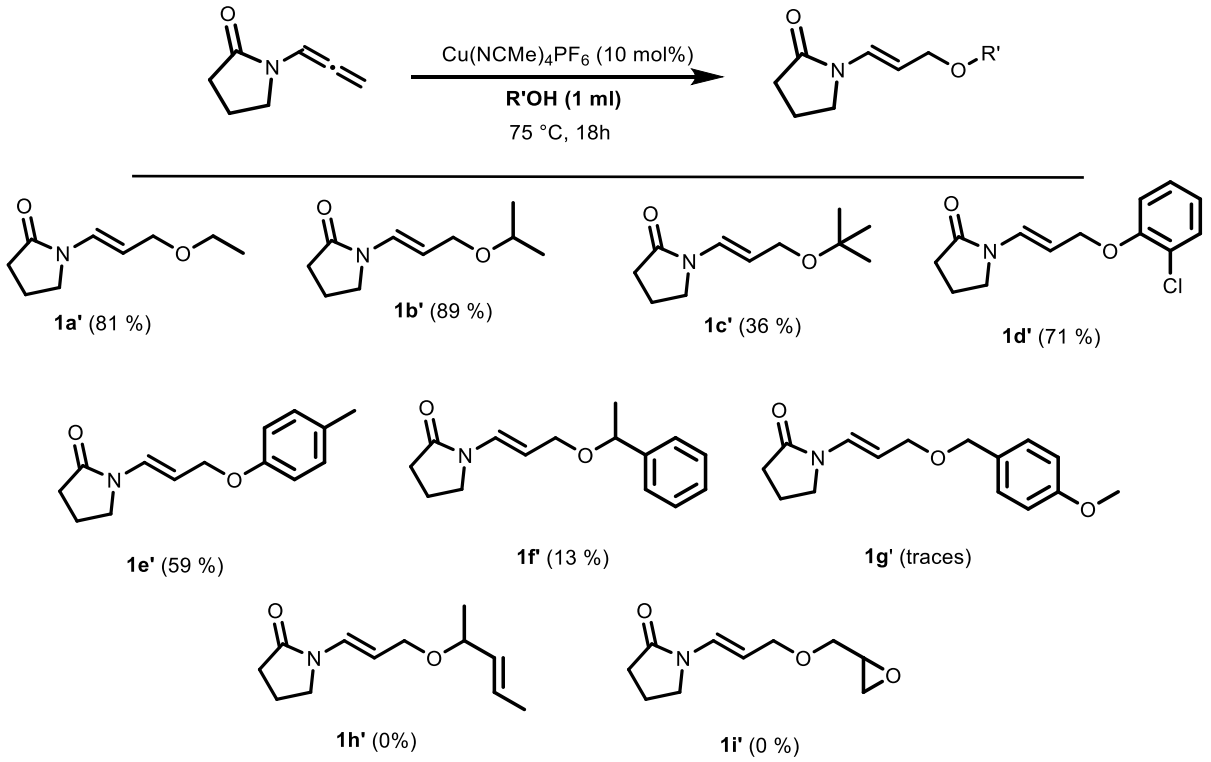


Entry	Catalyst	Yield %[a]
1	$[Cu(MeCN)_4]PF_6$	78
2	$[Cu(MeCN)_4]BF_4$	77
3	CuOAc	18
4	CuCN	0
5	CuTc	traces
6	CuBr	0

Reaction carried out with 0.5 mmol of allene, 0.05 mmol of copper salt in 1 ml of ethanol under an inert atmosphere, stirred at 75 °C for 18 hours. [a] Yield evaluated by ^{1}H NMR with 1,3,5-trimethoxybenzene as internal standard.

Meanwhile, we tested the reaction with different liquid alcohols as solvent and reagent to see the scope of this method (Scheme 99). The reaction with isopropanol affords the allylic product **1b'** in good yield (89%), whereas the one with *tert*-butanol gave only 36% of **1c'**. It is worthy to note that in this

reaction, allene was totally converted, and we did not detect any byproduct. The hydroalkoxylation in aromatic phenol such as 2-chlorophenol and *p*-cresol was achieved with good yields (71 and 59% respectively for **1d'**and **1e'**). The reactivity with benzyl alcohol like 1-phenylethan-1-ol and (4-methoxyphenyl)methanol was very bad yielding only 13% of **1f'** and traces of **1g'**. The reaction in (*E*)-pent-3-en-2-ol and oxiran-2-ylmethanol did not afford the desired product (0% for both **1h'** and **1i'**).

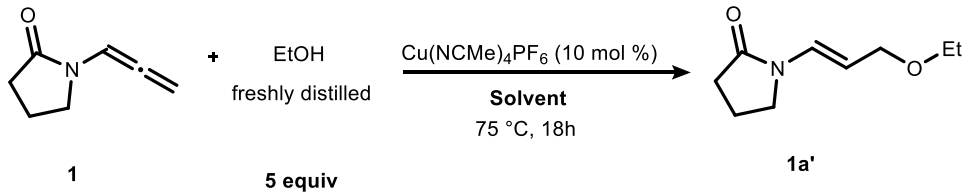


Scheme 99 : hydroalkoxylation with different alcohols.

These preliminary tests are interesting. The main drawback is the exclusive application of this method on the liquid alcohols due to the use of the latter as solvent. Our next step was to find a solvent that can be compatible to this reaction. That can extend the scope of this method with solid alcohols.

With 5 equiv of freshly distilled ethanol, we tested different solvent (Table 23). The admitted concentration was 0.5 mol. The reaction of *N*-allenyl-pyrrolidinone **1** with ethanol in ethers such as 1,4-dioxane, 2-methyltetrahydrofurane and THF afforded the product **1a'** in moderate to low yields respectively 24, 26 and 18% (Entries 2-4). We also set up a reaction in *t*-BuOH (Entry 5). **1a'** was formed with 30% of yield, and we did not detect any traces of *t*-BuOH addition on the allene. Using trifluorotoluene as solvent did not show any good effect and a poor yiled of **1a'** was formed (Entry 6, 13%). While the reaction in chlorinated solvents such as DCM and DCE or in a coordinating solvent like acetonitrile was ineffective : only traces of product were formed (Entries 7-9). The reactions in DMF and DMSO yielded **1a'** with respectively 49 and 35% (Entries 10-11). Indeed, DMF appeared to be the best solvent for this reaction among all the tested solvents.

Table 23 : tests in different solvents.



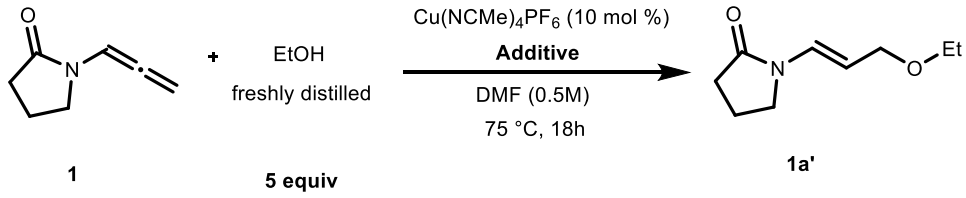
1 — 5 equiv — 1a'

Entry	Solvent	Yield %[a]
1	EtOH	78
2	dioxane	24
3	2-methyltetrahydrofuran	26
4	THF	18
5	*t*-BuOH	30
6	trifluorotoluene	13
7	DCM	traces
8	DCE	traces
9	Acetonitrile	traces
10	DMF	49
11	DMSO	35

Reaction carried out with 0.5 mmol of allene, 2.5 mmol of ethanol, 0.05 mmol of copper salt in 1 ml of solvent under an inert atmosphere, stirred at 75 °C for 18 hours. [a] Yield evaluated by ^{1}H NMR with 1,3,5-trimethoxybenzene as internal standard.

Using DMF, we tried to obtain better reaction conditions by adding a ligand, to check if it can improve the catalytic acitvity (Table 24). The presence of bipyridine blocked completly the catalytic activity of copper and the allenamide was totally recovered after the reaction (Entries 2-3). Adding a base to the reaction, has a negative impact on the reaction and we lost the reactivity. As well when we add a catalytic amount of silver triflate as co-catalyst, we did not detect any traces of **1a'** (Entry 6).

Table 24 : effect of some additives on the formation of **1a'**.



1 — 5 equiv — 1a'

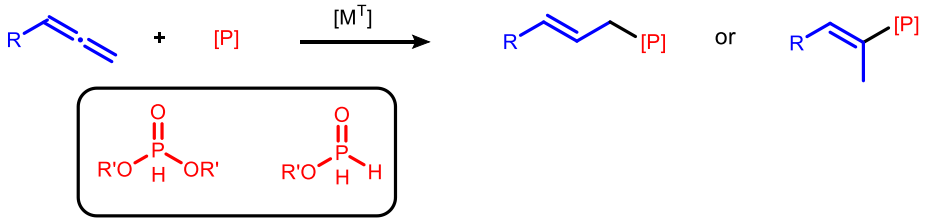
Entry	Additive	Yield %[a]
1	-	49
2	10 mol% bipyridine	0
3	20 mol% bipyridine	0
4	10 mol % NaH	0
5	1 equiv NaH	0
6	10 mol% of AgOtf	0

Reaction carried out with 0.5 mmol of allene, 2.5 mmol of ethanol, 0.05 mmol of copper salt, x mmol of additive in 1 ml of DMF under an inert atmosphere, stirred at 75 °C for 18 hours. [a] Yield evaluated by ^{1}H NMR with 1,3,5-trimethoxybenzene as internal standard.

This project will be definitely followed in the laboratory to find the best conditions and to extend the scope on the maximum of solid and liquid alcohols because it represents a cheap and direct alternative way to produce selectively allylic ethers.

IV. Intermolecular hydrophosphorylation of allenes

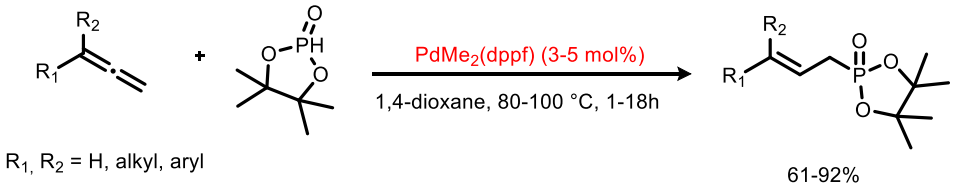
Allenes hydrophosphorylation is a method to create new C-P bond through the direct addition of phosphorylated compounds. This type of hydrofunctionalization was not widely studied like the hydroamination, and hydroarylation of allenes. Only few examples were reported in the litterature by using palladium or nickel catalysts (Scheme 100).



Scheme 100 : metal-catalyzed hydrophophorylation of allenes.

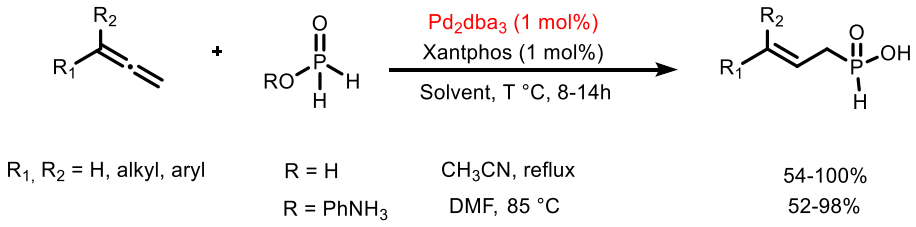
1. State of the art

In 2000, Tanaka's group developed a palladium-based catalytic system for the intermolecular hydrophosphorylation of terminal allenes.[169] Using 3 to 5 mol % of $PdMe_2$(dppf) they realized the selective addition of a 5-membered cyclic phosphonate on the terminal carbon. The allylic phosphonate product was obtained in good to excellent yield with a mixture of *E*/*Z* for the cases of monosubstituted allenes (Scheme 101).



Scheme 101 : palladium-catalyzed hydrophosphorylation of allenes.

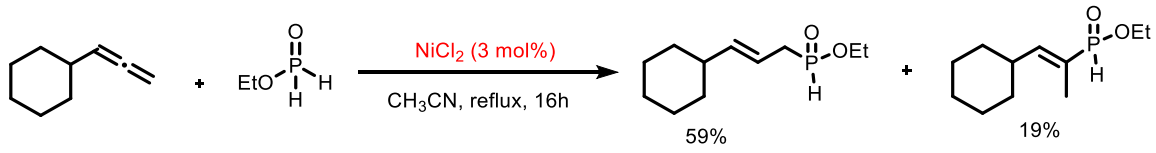
In 2008, Montchamp and coworkers reporteded the hydrophosphinylation by using palladium as catalyst, to achieve the addition of the hypophosphorous acid and its anilinium salt on terminal allenes.[170] After an acidic workup the allylic-*H*-phosphinic acid was obtained in good to excellent yield with a high *E*-selectivity (Scheme 102).



Scheme 102 : palladium-catalyzed allylation of phosphinic acid.

[169] C.-Q. Zhao, L.-B. Han, M. Tanaka, *Organometallics*, **2000**, 19, 4196.
[170] K. Bravo-Altamirano, I. Abrunhosa-Thomas, J.-L. Montchamp, *J. Org. Chem.* **2008**, 73, 2292.

Nickel has also been employed in the hydrophosphinylation of cyclohexylallene as a single example. It was reported by Montchamp.[171] Using 3 mol% of nickel chloride, they realized the addition of an alkyl phosphinate to afford a mixture of the allylic product and the branched one which is resulting from the addition on the central carbon in a ratio 3 : 1 (Scheme 103).

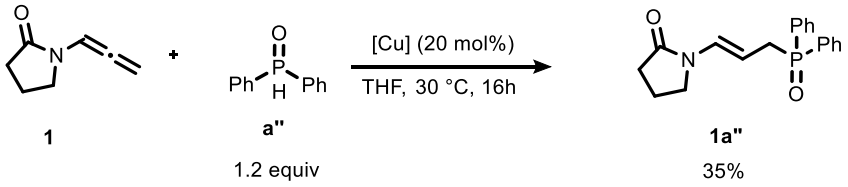


Scheme 103 : nickel-catalyzed hydrophosphinylation of cyclohexylallene.

In this part, our goal was to create a new C-P bond from allene with high regio- and stereoselectivity by using a copper catalytic system.

2. Preliminary tests

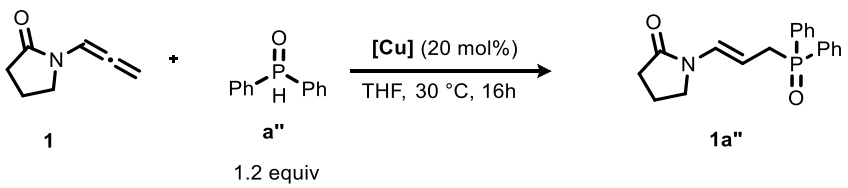
As previously described, we started with *N*-allenyl-pyrrolidinone to develop a hydrophosphorylation method and to apply it on different phosphorus nucleophiles to form allylphosphoric derivatives. We chose the diphenyl phosphine oxide as model substrate. We realized the first test with 20 mol% of copper iodide in THF (Scheme 104). After 16 hours of reaction at 30 °C, the desired allylic product was obtained in 35%. This yield was evaluated by NMR in presence of 1,3,5-trimethoxybenzene as internal standard.



Scheme 104 : initial attempt.

Under these conditions, we realized a blank test to verify the necessity of the copper for the hydrophosphorylation (Table 25). In absence of CuI, we recovered completly the allene and the reactivity of our system was completly lost (Entry 2). which proved the importance of the copper to promote this reaction. Based on this result, we tested different copper salts. The reaction in presence of 20 mol% of CuBr gave similar yield as CuI (Entry 3). While, a test with $(CuOTf)_2$.toluene as copper source affords 81% of **1a''** (Entry 4). A test in presence of $Cu(CH_3CN)_4PF_6$ give the allylic product **1a''** in good yield (Entry 5, 60%). So, for the following tests we used $Cu(CH_3CN)_4PF_6$ as best catalyst for the reaction.

Table 25 : tests with different copper salts.



Entry	Catalyst	Yield %[a]

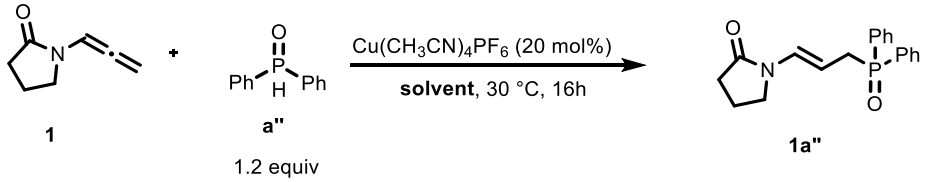
[171] P. Ribière, K. Bravo-Altamirano, M. I. Antczak, J. D. Hawkins, J.-L. Montchamp, *J. Org. Chem.* **2005**, 70, 4064

1	CuI	35
2	-	0
3	CuBr	32
4	$(CuOTf)_2$.toluene	81
5	$Cu(CH_3CN)_4PF_6$	60

Reaction carried out with 0.5 mmol of allene, 0.6 mmol of diphenylphosphine oxide, 0.1 mmol of copper salt in 1 ml of THF under an inert atmosphere, stirred at 30 °C for 16 hours. [a] Yield evaluated by ^{1}H NMR with 1,3,5-trimethoxybenzene as internal standard.

The following tested parameter was the solvent (Table 26). As THF gave good yield (60%), we started by testing ether solvents to see their influence on the reactivity. As expecting, the reaction in 1,4-dioxane gave the product **1a''** in 88% (Entry 2). Whereas, the reaction in 2-methyltetrahydrofurane did not improve the yield (Entry 3, 57%).

Table 26 : solvents effect on the formation of 1a''.

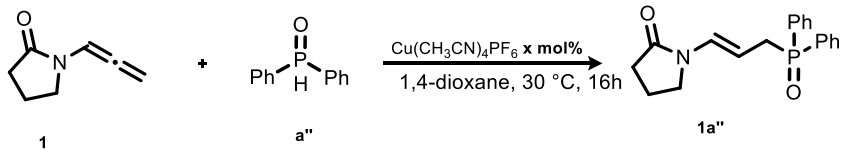


Entry	Solvent	Yield %[a]
1	THF	60
2	1,4-dioxane	88
3	2-methyltetrahydrofurane	57

Reaction carried out with 0.5 mmol of allene 1, 0.6 mmol of diphenylphosphne oxide, 0.1 mmol of $Cu(CH_3CN)_4PF_6$ in 1 ml of solvent under an inert atmosphere, stirred at 30 °C for 16 hours. [a] Yield evaluated by ^{1}H NMR with 1,3,5-trimethoxybenzene as internal standard.

With the good yield obtained in 1,4-dioxane, we were looking to lower the catalytic charge (Table 27). When we decreased the catalytic charge from 20 to 15 mol% the loss in the yield was not significatif, and **1a''** was formed in good yield (Entry 2, 84%). Even, when we used only 10 mol% of $Cu(CH_3CN)_4PF_6$ the yield was good (Entry 3, 81%).

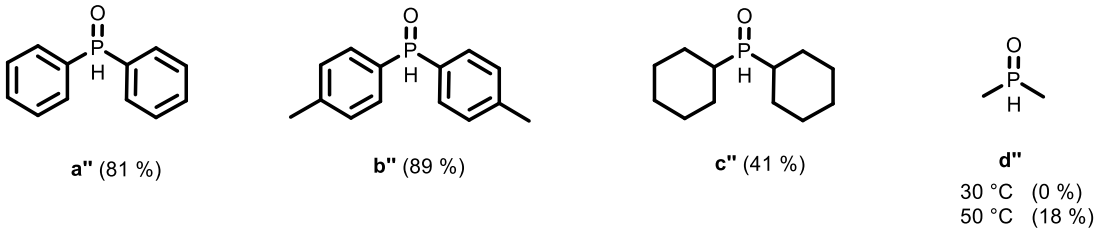
Table 27 : effect of the copper charge.



Entry	x mol%	Yield %[a]
1	20	88
2	15	84
3	10	81

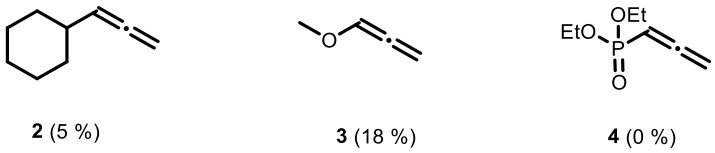
Reaction carried out with 0.5 mmol of allene 1, 0.6 mmol of diphenylphosphine oxide a'', x mol% of $Cu(CH_3CN)_4PF_6$ in 1 ml of 1,4-dioxane under an inert atmosphere, stirred at 30 °C for 16 hours. [a] Yield evaluated by ^{1}H NMR with 1,3,5-trimethoxybenzene as internal standard.

Based on the tested parameters, we began to test this reactivity on many phosphine oxide derivatives (Scheme 105). The reaction of di(*p*-tolyl)phosphine oxide **b''** with the allene afford the allylic product in excellent yields (89%). Albeit, it seems that the dialkylphosphine oxides are not suitable for this reaction. When we tested dicyclohexylphosphine oxide **c''**, the hydrophosphorylation occured and gave only 41 % of the product. Dimethylphosphine oxide **d''** was totally inactive for this reaction at 30 °C. While, the same reaction at 50 °C yields 18% of the allylic product.



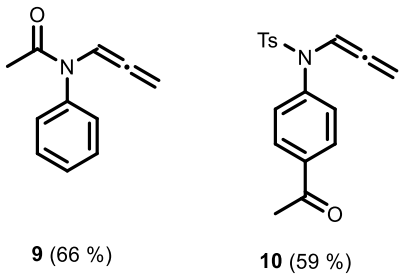
Scheme 105 : hydrophosphorylation with different phosphine oxides.

Meantime, we began to test the reactivity of various allenes with diphenylphosphine oxide under these conditions (Scheme 106). Cyclohexyl- and methoxyallene (**2** and **3**) showed a weak reactivity and afforded the hydrophosphorylate product with a poor yields, respectively 5 and 18%. Allenyl phosphonate **4** did not react, and it was recovered completly after 16 hours.



Scheme 106 : hydroarylation of different allenes.

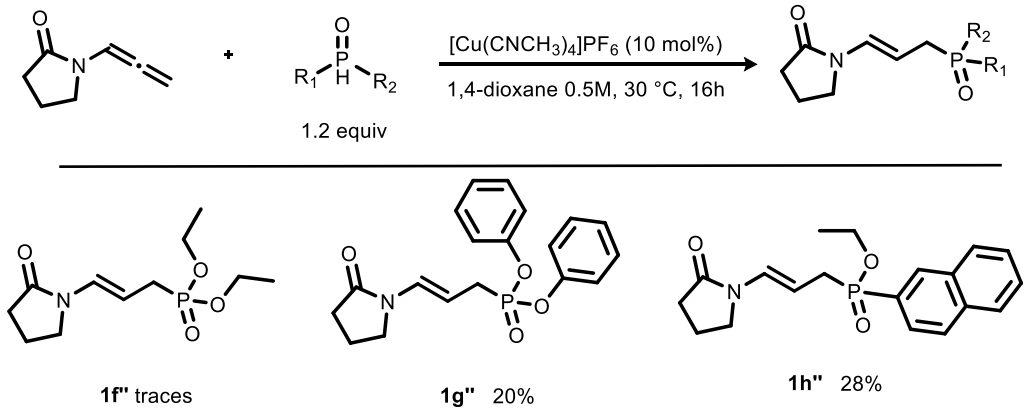
The hydrophosphorylation of the *N*-allenamide **9** and the allenyl sulfonamide **10** (Scheme 107) with 1,3,5-trimethoxybenzene afforded selectively the allylic product with moderate to good yields (respectively 66 and 59%).



Scheme 107 : hydroarylation of allenyl amide and sulfonamide.

Encouraged by these results, and in the same time by the extend of the hydrophosphorylation method with secondary phosphine oxide, we aimed to apply this kind of functonalization on dialkyl and diaryl phosphites.

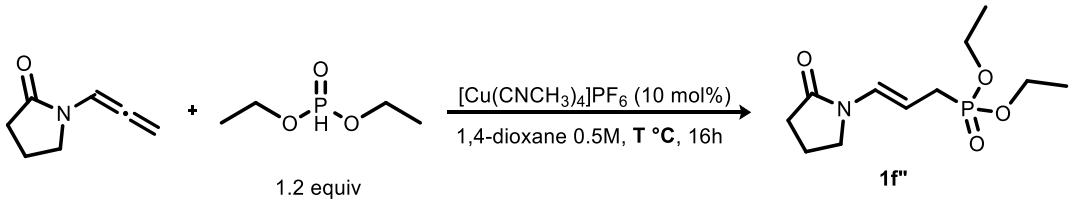
Based on the conditions cited above and used for the allylation of phosphine oxide, we started our preliminary tests (Scheme 108). By using 10 mol% of $Cu(CH_3CN)_4PF_6$ in dioxane, we tested different phosphorus compounds. When we set up the reaction at 30 °C, the reactivity of diethyl and diphenyl phosphite and ethyl naphthalen-2-ylphosphinate was very low affording very poor yield respectively traces, 20 and 28% of the desired products.



Scheme 108 : allylation of organophosphorus compounds.

In ordre to increase this reactivity, we chose diethyl phosphite as model to realize some supplement tests. First, we began by increasing the temperature to see its effect (Table 28). When the reaction is carried out at 50 °C, the product **1f''** was obtained with 19 % (Entry 2). Exceeding the boiling point of the diethyl phosphite, we set up a reaction at 100 °C, **1f''** is formed with 27 % of yield with a total consumption of the organophosphorus reagent (Entry 3). Therefore, the thermal tests were inefficient.

Table 28 : temperature effect on the reaction.

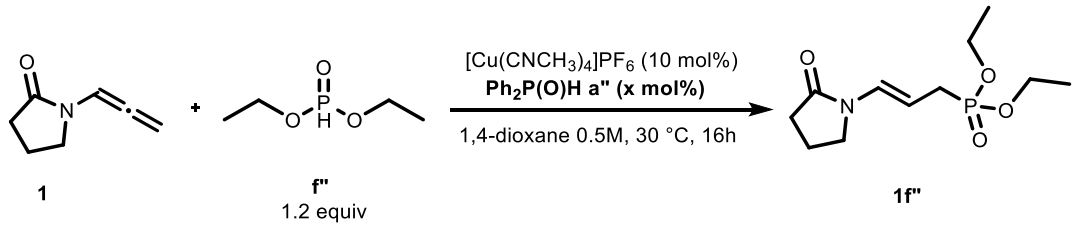


Entry	T °C	Yield %[a]
1	30	traces
2	50	19
3	100	27

Reaction carried out with 0.5 mmol of allene 1, 0.6 mmol of diethylphosphite, 0.05 mmol of $Cu(CH_3CN)_4PF_6$ in 1 ml of 1,4-dioxane under an inert atmosphere, stirred at T°C for 16 hours. [a] Yield evaluated by ^1H NMR with 1,3,5-trimethoxybenzene as internal standard.

We were surprised by the reactivity of phosphite compounds comparing to the diphenylphosphine oxide, mainly because they are more nucleophiles than the latter one. We were wondering if in the case of diphenyl phosphine oxide, the copper ions formed with the first one a complex that can promote and catalyze the hydrophosphorylation of the allene. So, we proceeded some tests in presence of catalytic amount of diphenylphosphine oxide (Table 29). When we used 10 mol% of **a''**, the allene was completely recovered ater 16h. While, using 20 mol% of **a''** (corresponding to a ratio 2 :1 with the metal center) we detected a weak improvement and and **1f''** was formed with 27% of yield. It is worthy to note that we did not obtain in these tests (Entries 2-3) any traces of **1a''**.

Table 29 : tests in presence of diphenylphosphine oxide.

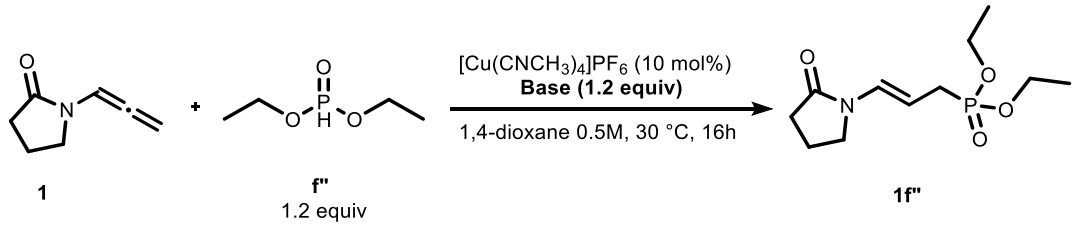


Entry	a'' (x mol%)	Yield %[a]
1	0	traces
2	10	0
3	20	27

Reaction carried out with 0.5 mmol of allene 1, 0.6 mmol of diethylphosphite, 0.05 mmol of $Cu(CH_3CN)_4PF_6$, x mol% of a'' in 1 ml of 1,4-dioxane under an inert atmosphere, stirred at 30°C for 16 hours. [a] Yield evaluated by ^1H NMR with 1,3,5-trimethoxybenzene as internal standard.

In parallel, we proposed to increase the nucleophilicity of the diethyl phosphite. So, we tested several bases such as triethyl amine, sodium hydroxide, potassium and lithium bis(trimethylsilyl)amide (Table 30). But all these trials failed and did not afford the desired product (Entries 2-5).

Table 30 : base effect on the reaction.



Entry	Base	Yield %[a]
1	-	traces
2	Et_3N	0
3	NaH	0
4	KHMDS[b]	0
5	LiHMDS[b]	0

Reaction carried out with 0.5 mmol of allene 1, 0.6 mmol of diethylphosphite, 0.05 mmol of $Cu(CH_3CN)_4PF_6$, 1.2 equiv of base in 1 ml of 1,4-dioxane under an inert atmosphere, stirred at 30°C for 16 hours. [a] Yield evaluated by ^1H NMR with 1,3,5-trimethoxybenzene as internal standard.

The conditions optimization is not finished yet, we are looking to find a solution for the addition of phosphite and phosphinate derivatives.

So, using copper catalytic system we are able to produce selectively allylphosphonate derivatives. The latter present high value in chemistry. They constitute key intermediates for the synthesis of diene, valuable skeletons in the organic and pharmaceutical chemistry, through an olefination reaction with carbonyl derivatives.

V. Experimental part

General considerations

All reactions were performed in oven-dried Schlenk flasks under an atmosphere of argon closed with Rodavis® Screw caps. Tetrakis(acetonitrile)copper(I) hexafluorophosphate was purchased from Strem chemicals , used as received, stored in a desiccator cabinet and weighed to air. Allenes were prepared following methods described in the litterature.[172] Aryls and heteroaromatics were purchased from either Sigma-Aldrich® or Alfa Aesar® or Acros Organics® and used as received. Dry acetonitrile was used for these reaction.

^{1}H and ^{13}C NMR spectra were recorded with a Bruker AC-400 MHz spectrometer in $CDCl_3$. For ^{1}H NMR (400 MHz), $CHCl_3$ and TMS served as internal standards (δ = 7.26 for $CHCl_3$ and 0 ppm for TMS) and data are reported as follows: chemical shift (in ppm), multiplicity (s = singlet, bs = broad singlet, d = doublet, t = triplet, q = quartet, dd = doublet of doublets, dt = doublet of triplets, td = triplet of doublets, ddd = doublet of doublet of doublets, m = multiplet), coupling constant (in Hz), and integration. For ^{13}C NMR (100 MHz), $CHCl_3$ was used as internal standards (δ = 77.6 ppm) and spectra were obtained with complete proton decoupling. Gas chromatography–mass spectra (GC-MS) were recorded on a Shimadzu QP2012-SE with a Zebron ZB-5MS (20m × 0,18mm), capillary apolar column (Stationary phase: 0.18 µm film). GC-MS method: Initial temperature: 50°C; Initial time: 2 min; Ramp: 22°C/min; Final Temperature: 280°C; Final time: 15min or 23min. HRMS (Q-TOF) were performed on a JEOL JMS-DX300 spectrometer (3 keV, xenon) in a m-nitrobenzyl alcohol matrix. Melting points were measured using Stuart SMP50 Automatic Melting point.

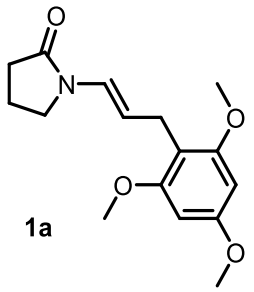
In this exeperimental part, we present only the general procedure of the hydroarylation as it is the most reaction advanced among the three hydrofunctionnalizations cited in this chapter.

General procedure for the allene hydroarylation

An oven-dried Schlenk flask of appropriate size equipped with a magnetic stirring bar is placed under vacuum then back-filled with argon. This procedure is repeated three times. Under a stream of argon, $Cu(CH_3CN)_4PF_6$ (10 mol %) is added, followed by acetonitrile (1 mL) and the allene (0.5 mmol, 1 equiv). After a stirring for 10 minutes, the (hetero)-aromatic is finally added (0.6 mmol, 1.2 equiv). The Schlenk is sealed under a positive pressure of argon, stirred and heated at 100 °C for 16h. After allowing the reaction to cool to room temperature, 4-bromoanisole (0.05 mmol, 0.1 equiv) dissolved in dichloromethane is added as internal standard. Solvent was evaporated under vacuum after one aqueous washing. The residue is purified by triethylamine treated silica gel column chromatography.

Experimental procedures and characterization data

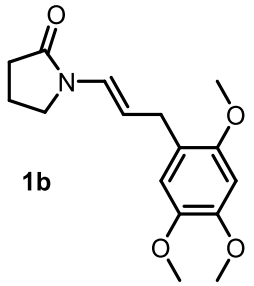
[172] T. W. Bousfield, M. C. Kimber, *Tetrahedron. Lett*. **2015**, 56, 350



(*E*)-1-(3-(2,4,6-trimethoxyphenyl)prop-1-en-1-yl)pyrrolidin-2-one **1a**

The reaction of *N*-Allenyl-2-pyrrolidinone (**1**, 76 µl, 0.5 mmol) with 1,3,5-trimethoxybenzene (**a**, 101 mg, 0.6 mmol) using $Cu(CH_3CN)_4PF_6$ (20 mg, 10 mol %) heated at 100 °C according to general procedure gave the title compound **1a** in the form of a colorless oil (122 mg, 84 %) (flash chromatography eluent: gradient Pentane/ ethyl acetate 90:10).

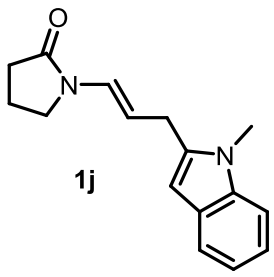
^{1}H NMR (400 MHz, $CDCl_3$) δ 6.93 (d, *J* = 14.4 Hz, 1H), 6.12 (s, 2H), 5.04 (dt, *J* = 14.4, 7.0 Hz, 1H), 3.80 (s, 6H), 3.79 (s, 3H), 3.55 – 3.41 (m, 2H), 3.32 (dd, *J* = 7.0, 1.2 Hz, 2H), 2.43 (t, *J* = 8.1 Hz, 2H), 2.13 – 1.93 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 172.68, 171.05, 159.62, 158.66, 123.71, 111.07, 109.44, 90.68, 55.78, 55.37, 45.33, 31.44, 23.21, 17.48. HRMS (ESI) m/z: [M+H]+ Calcd for $C_{16}H_{22}NO_4$ 292.1549; Found 292.1549.



(*E*)-1-(3-(2,4,5-trimethoxyphenyl)prop-1-en-1-yl)pyrrolidin-2-one **1b**

The reaction of *N*-Allenyl-2-pyrrolidinone (**1**, 76 µl, 0.5 mmol) with 1,2,4-trimethoxybenzene (**b**, 90 µl, 0.6 mmol) using $Cu(CH_3CN)_4PF_6$ (20 mg, 10 mol %) heated at 100 °C according to general procedure gave the title compound **1b** in the form of a white solid (131 mg, 90%) (flash chromatography eluent: gradient cyclohexane/ ethyl acetate 70:30).

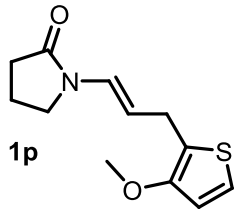
^{1}H NMR (400 MHz, $CDCl_3$) δ 6.95 (d, *J* = 14.4 Hz, 1H), 6.67 (s, 1H), 6.51 (s, 1H), 5.05 (dt, *J* = 14.4, 7.1 Hz, 1H), 3.86 (s, 3H), 3.81 (s, 3H), 3.79 (s, 3H), 3.47 (t, *J* = 8.1 Hz, 2H), 3.31 (d, *J* = 7.1 Hz, 2H), 2.45 (t, *J* = 8.1 Hz, 2H), 2.13 – 2.00 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 172.89, 172.89, 151.24, 148.06, 143.06, 124.19, 120.57, 114.01, 110.96, 97.96, 56.71, 56.48, 56.25, 45.29, 31.28, 30.16, 17.42. HRMS (ESI) m/z: $[M+Na]^+$ Calcd for $C_{16}H_{21}NO_4Na$ 314.1368; Found 314.1376.



(*E*)-1-(3-(1-methyl-1H-indol-2-yl)prop-1-en-1-yl)pyrrolidin-2-one **1j**

The reaction of *N*-Allenyl-2-pyrrolidinone (**1**, 76 µl, 0.5 mmol) with *N*-methylindole (**j**, 75 µl, 0.6 mmol) using $Cu(CH_3CN)_4PF_6$ (20 mg, 10 mol %) heated at 100 °C according to general procedure gave the title compound **1j** in the form of a brown oil (92 mg, 73 %) (flash chromatography eluent: gradient petroleum ether/ diethyl ether 70:30).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.64 – 7.56 (m, 1H), 7.31 – 7.27 (m, 1H), 7.22 (ddd, *J* = 8.2, 7.0, 1.2 Hz, 1H), 7.09 (ddd, *J* = 12.8, 7.0, 3.5 Hz, 2H), 6.84 (s, 1H), 5.17 (dt, *J* = 14.2, 7.1 Hz, 1H), 3.74 (s, 3H), 3.54 (dd, *J* = 7.1, 2.2 Hz, 2H), 3.49 (t, *J* = 8.2 Hz, 2H), 2.48 (t, *J* = 8.2 Hz, 2H), 2.08 (dt, *J* = 16.0, 7.5 Hz, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 172.94, 137.22, 136.26, 127.64, 126.45, 124.57, 124.10, 122.17, 121.65, 120.51, 119.09, 118.81, 118.79, 113.65, 111.46, 111.37, 109.23, 45.36, 32.62, 31.33, 26.09, 17.50.

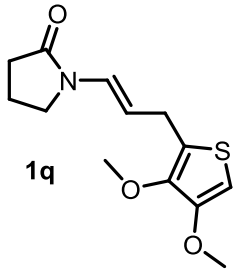


1p

(*E*)-1-(3-(3-methoxythiophen-2-yl)prop-1-en-1-yl)pyrrolidin-2-one **1p**

The reaction of *N*-Allenyl-2-pyrrolidinone (**1**, 76 µl, 0.5 mmol) with 3-methoxythiophene (**p**, 60 µl, 0.6 mmol) using $Cu(CH_3CN)_4PF_6$ (20 mg, 10 mol %) heated at 100 °C according to general procedure gave the title compound **1p** in the form of a yellow oil (84 mg, 71 %) (flash chromatography eluent: gradient petroleum ether/ ethyl acetate 70:30).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.02 – 7.00 (d, *J* = 14.3 Hz, 1H), 6.97 (d, *J* = 5.5 Hz, 1H), 6.80 (d, *J* = 5.5 Hz, 1H), 5.05 (dt, *J* = 14.3, 7.1 Hz, 6H), 3.81 (s, 3H), 3.49 (t, *J* = 8.2 Hz, 13H), 3.45 (dd, *J* = 7.1, 1.3 Hz, 2H), 2.46 (t, *J* = 8.2 Hz, 2H), 2.13 – 2.00 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 173.01, 153.30, 124.67, 120.92, 116.72, 110.15, 58.94, 45.24, 31.24, 26.27, 17.42.



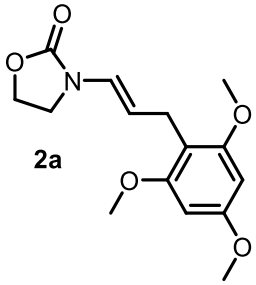
1q

(*E*)-1-(3-(3,4-dimethoxythiophen-2-yl)prop-1-en-1-yl)pyrrolidin-2-one **1q**

The reaction of *N*-Allenyl-2-pyrrolidinone (**1**, 76 µl, 0.5 mmol) with 3,4-dimethoxythiophene (**q**, 72 µl, 0.6 mmol) using $Cu(CH_3CN)_4PF_6$ (20 mg, 10 mol %) heated at 100 °C according to general procedure gave the title compound **1q** in the form of a brown oil (117 mg, 88 %) (flash chromatography eluent: gradient pentaneether/ diethyl ether 70:30 to 50 :50).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.01 (d, *J* = 14.3 Hz, 1H), 5.99 (s, 1H), 5.02 (dt, *J* = 14.3, 7.0 Hz, 1H), 3.81 (s, 3H), 3.80 (s, 3H), 3.50 (t, *J* = 8.1 Hz, 2H), 3.46 (dd, *J* = 7.0, 1.3 Hz, 2H), 2.48 (t, *J* = 8.1 Hz, 2H), 2.13 – 2.03 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 173.09, 150.73, 143.24, 125.89, 125.08, 109.45, 92.91, 60.93,

57.10, 45.26, 31.26, 27.24, 17.47. HRMS (ESI) m/z: $[M+Na]^+$ Calcd for $C_{13}H_{17}NO_3SNa$ 290.0827; Found 290.0832.



2a

(*E*)-3-(3-(2,4,6-trimethoxyphenyl)prop-1-en-1-yl)oxazolidin-2-one **2a**

The reaction of *N*-Allenyl-2-oxazolidinone (**2**, 62.5 mg, 0.5 mmol) with 1,3,5-trimethoxybenzene (**a**, 101 mg, 0.6 mmol) using $Cu(CH_3CN)_4PF_6$ (20 mg, 10 mol %) heated at 100 °C according to general procedure gave the title compound **2a** in the form of a brown oil (94 mg, 64 %) (flash chromatography eluent: gradient petroleum ether/ diethyl ether 70:30).

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.67 (d, *J* = 14.2 Hz, 1H), 6.13 (s, 2H), 4.91 (dt, *J* = 14.2, 6.9 Hz, 1H), 4.36 (dd, *J* = 8.9, 7.3 Hz, 2H), 3.80 (d, *J* = 2.0 Hz, 9H), 3.67 – 3.62 (m, 2H), 3.31 (dd, *J* = 6.9, 1.2 Hz, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 158.65, 123.98, 109.96, 109.30, 109.09, 90.65, 62.20, 56.09, 55.36, 42.64, 22.66.

Chapter IV :

Direct amination of phenols *via* ruthenium π-complexes

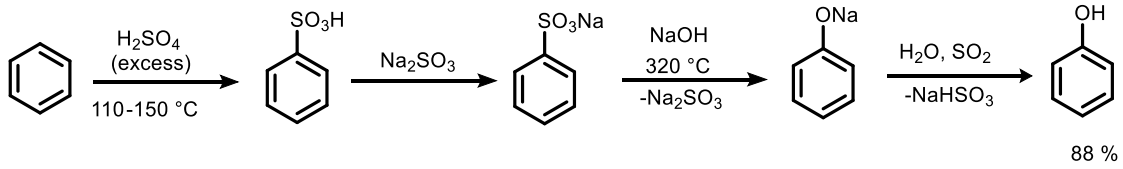
I. Introduction

Phenol or hydroxybenzene was discovered by Johann Rudolf Glauber in 1650 from coal tar. It was isolated in a pure form for the first time in 1841 by Auguste Laurent and he called it phenic acid.[173] Phenol was one of the first antiseptic used in medicine by Sir Joseph Lister in 1865.[174]

1. Production of phenol

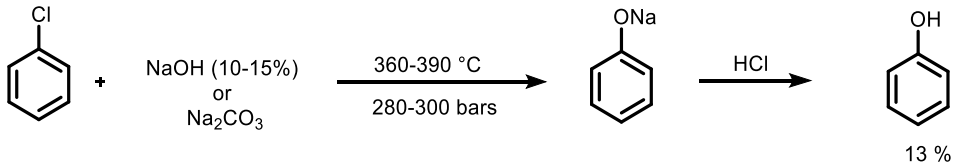
Phenol is one of the most abundant aromatics feedstocks especially in coal tar. In addition, it is one of the basic unit of the lignin, in a form of cross-linked polymer. Despite its abundance, the recoverable quantities are not enough, and phenol is produced *via* several industrial processes.

Since 1900's, many procedures have been used to manufacture the phenol. It started when Bayer and Monsanto developed the phenol synthesis *via* benzene sulfonylation (Scheme 109). [175] Benzene reacts with an excess of H_2SO_4 or oleum (H_2SO_4 + SO_3) at 110-150 °C and affords benzenesulfonic acid which is neutralized with Na_2SO_3 thus yielding the corresponding sodium salt. The latter react in presence of NaOH at 320 °C to form sodium phenolate and generate sodium sulfite. Finally, addition of SO_2 leads to the formation of phenol with 88% of yield after distillation.



Scheme 109 : phenol synthesis from via benzene sulfonylation.

Other routes for phenol synthesis were based on chlorobenzene. Dow and Bayer used it as intermediate to synthesize phenols, by hydrolysis reaction with NaOH (10-15%) or Na_2CO_3 at high pressure (280-300 bars) and high temperature (360-390 °C). The phenol is obtained after acidic treatement treatment of sodium phenolate with HCl (Scheme 110).[176]



Scheme 110 : synthesis of phenol from chlorobenzene.

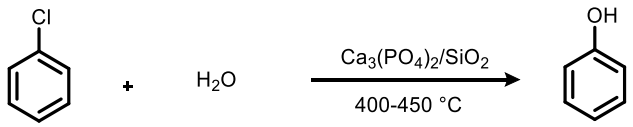
Raschig-Hooker process is also using chlorobenzene as intermediate to produce the phenol. The hydrolysis of chlorobenzene is catalyzed by tricalcium phosphate on silicon dioxide and it is carried out at 400-450 °C (Scheme 111). This procedure is still used in several countries like Italy, Poland, Argentina and India and it gives a similar yield as the previous one.[176]

[173] A. Laurent, *Mémoire sur le phényle et ses dérivés*, **1841**, 195.

[174] J. Lemaire, *De l'acide phénique, de son action sur les végétaux, les animaux, les ferments, les venins, les virus, les miasmes et de ses applications à l'industrie, à l'hygiène, aux sciences anatomiques et à la thérapeutique*, 2e éd. , **1865**.

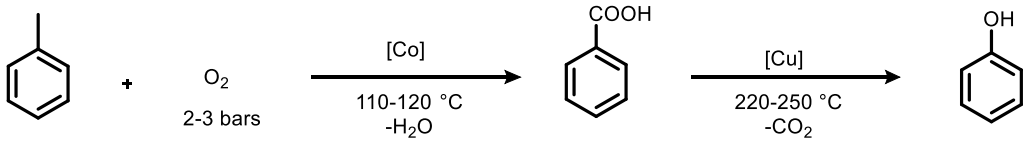
[175] H.A. Wittcoff, B.G. Reuben, Industrial Organic Chemicals in Perspective. Part One: Raw Materials and Manufacture. Wiley-Interscience, N. Y. **1980**.

[176] H. J. Arpe, *Industrial Organic Chemistry. Wiley-VCH*. 5th edition.



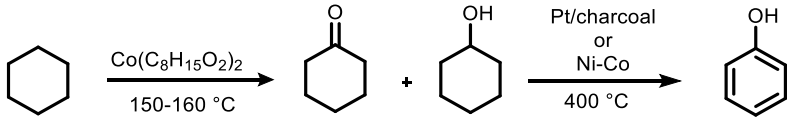
Scheme 111 : phenol synthesis *via* hydrolysis of chlorobenzene.

Alternative route for phenol production is the toluene oxidation. It is developed by Dow and California and occurs in two steps (Scheme 112). First, the toluene is oxidized in presence of cobalt salts, under a pressure of oxygen at 110-120 °C to yield the benzoic acid. The latter undergoes an oxidative decarboxylation in presence of copper (II) catalyst and air bubbling at high temperature, to afford phenol.[177]



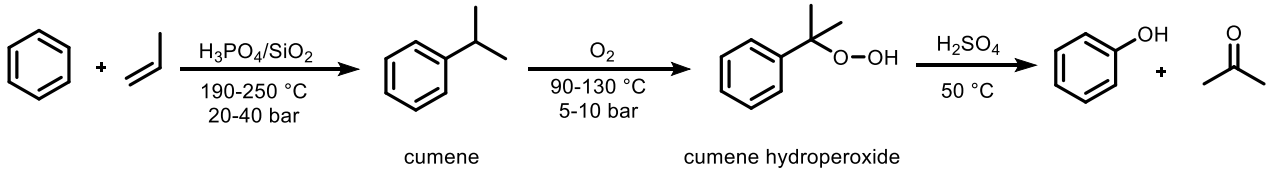
Scheme 112 : phenol synthesis *via* toluene oxidation.

Another method to obtain phenol is the oxidation of cyclohexane in presence of cobalt octanoate at 150-160 °C that affords a mixture of cyclohexanone and cyclohexanol. Both are dehydrogenated in presence of catalyst such as Pt/charcoal or a bimetallic mixture like Ni-Co at 400 °C to produce the phenol (Scheme 113).



Scheme 113 : phenol production from cyclohexane by oxidation and dehydrogenation.

In 1944, Hock and Lang discovered an efficient route for the phenol manufacturing through cumene intermediate and following three steps (Scheme 114). First, a Friedel-Crafts reaction between benzene and propene in presence of acid affords cumene. The latter is oxidized to give the cumene hydroperoxide. Then it undergoes an acid catalyzed cleavage yielding phenol and acetone as byproduct. In the last decades, Hock procedure became the most applied method for the phenol production throughout the world.[176]



Scheme 114 : phenol synthesis by Hock procedure.

From synthetic or naturel sources, the global annual production capacity of phenol reached 11.5 million tonnes in 2012 (Figure 30).[178]

[177] W. W. Kaeding, R. O. Lindblom, R. G. Temple, H. I. Mahon, *Ind. Eng. Chem. Process Des. Dev*. **1965**, 4, 97.

[178] "Global Phenol Supply to Exceed 10.7 Mln Tonnes in **2016**." *Merchant Research & Consulting, Ltd.*, mcgroup.co.uk/news/20140131/global-phenol-supply-exceed-107-mln-tonnes.html.

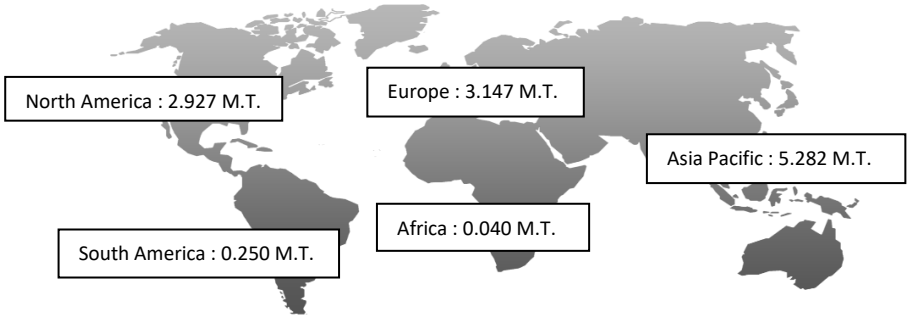


Figure 30 : phenol capacities across region in 2012.

2. World Phenol Application

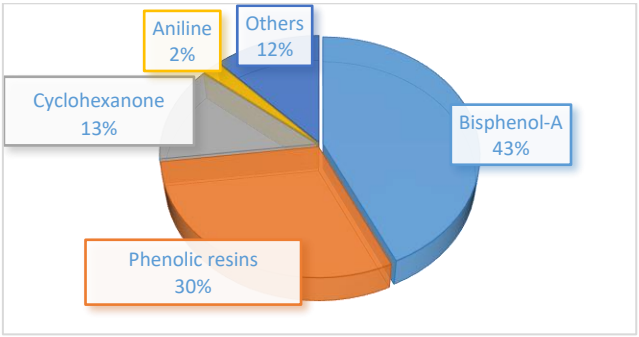
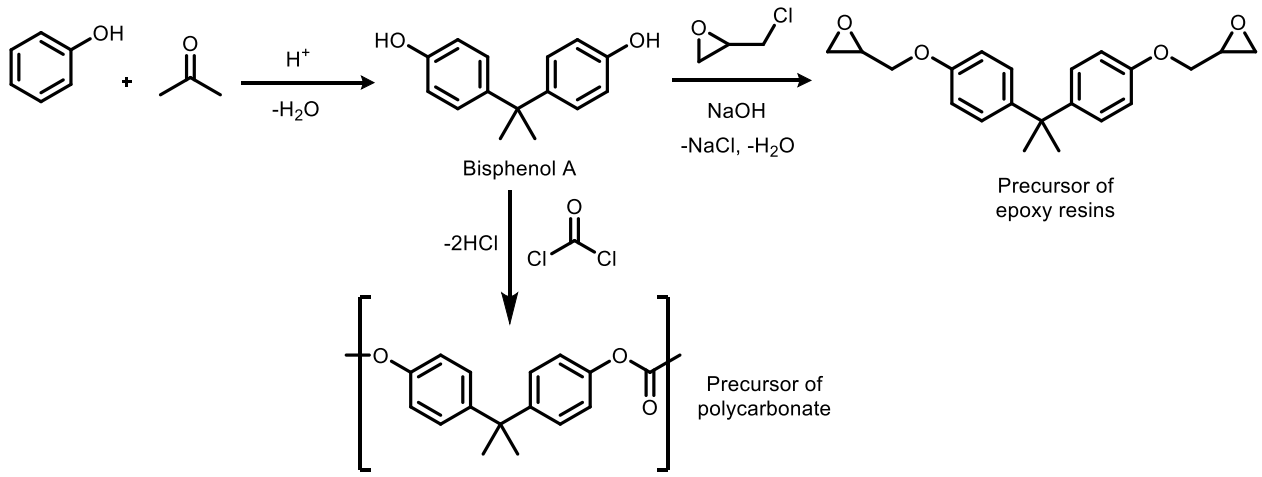


Figure 31 : world phenol application.

Bisphenol A or 2,2-Bis-(4-hydroxyphenyl)propane is the bigger consumer of phenol (43%). It is prepared by the condensation of 2 equivalents of phenol and 1 equivalent of acetone in presence of a strong acid (Scheme 115). It is the source of two significant applications: Polycarbonate and epoxy resins. Polycarbonates are obtained by the condensation of Bisphenol A with phosgene or by transesterification with dimethyl carbonate.[179] They are widely used in the electrical engineering and compact discs. While the reaction of bisphenol A with epichlorohydrin produces glycidyl ethers which is the base of epoxy resins used for example in the lining for some food cans.



Scheme 115 : synthesis of Bisphenol A from phenol and acetone.

[179] Serini, V. (2000). *Polycarbonates. Ullmann's Encyclopedia of Industrial Chemistry.*

Phenolic resins (Figure 32), a principal source of composite materials, are in the second place with 30% of global application.[180] They result from the polycondensation of phenol with formaldehyde. They are widely used for the production of paints, adhesives, foam plastics and molding materials.

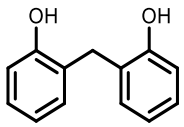
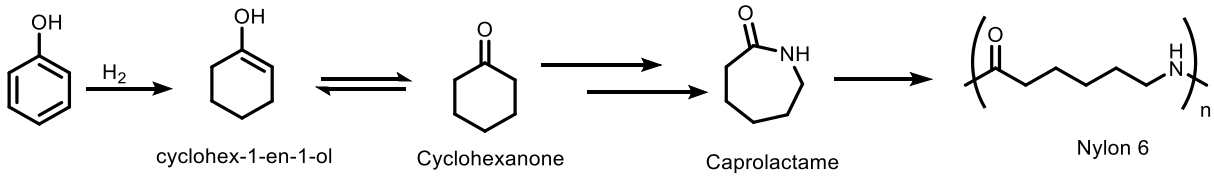


Figure 32 : the monomer of Phenolic resins.

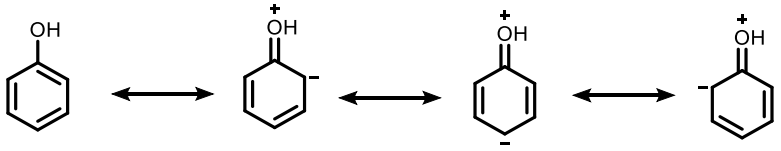
The last main application concerns nylon. The hydrogenation of phenol produces cyclohexanone, an important key precursor to nylon (Scheme 116). Phenol is also the source of many active molecules like drugs and herbicides (12%). Only 2% of the total production are used as aniline precursor, despite the high value of the last one (see Chapter II).



Scheme 116 : production of nylon 6 from phenol hydrogenation.

3. Caracteristics

The resonance energy of phenol is 167 KJ/mol while the one for benzene is 150 KJ/mol. This high value is due to the oxygen lone pair that can participate in the delocalization with the ring electrons (Scheme 117), making the phenol C-O bond shorter than the one for cyclohexanol for example.



Scheme 117 : resonance structures of phenol.

Phenols contain a high acidic hydroxyl group. Due to the π-conjugation they have a high dissociation energy for the C-O bond. Consequently, it is necessary to transform phenols to phenol derivatives (like sulfonates, esyers, ethers…) to remove the acidic proton and to decrease the energy of the C-O bond (Figure 33), which facilitate the functionalization of these compounds.

[180] R. M. Pandia, (**2013**), The phenol-acetone value chain: prospects and opportunities, [PowerPoint Slides]. Retrieved from https://www.platts.com/IM.Platts.Content/ProductsServices/ConferenceandEvents/2013/ga001/presentations/26Sept_16.25_%20Rajeev%20Pandia.pdf.

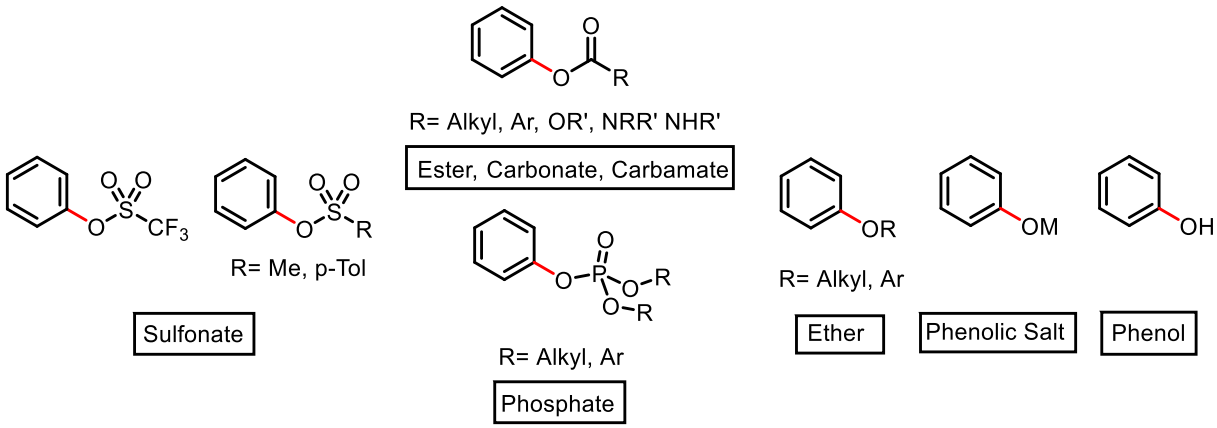
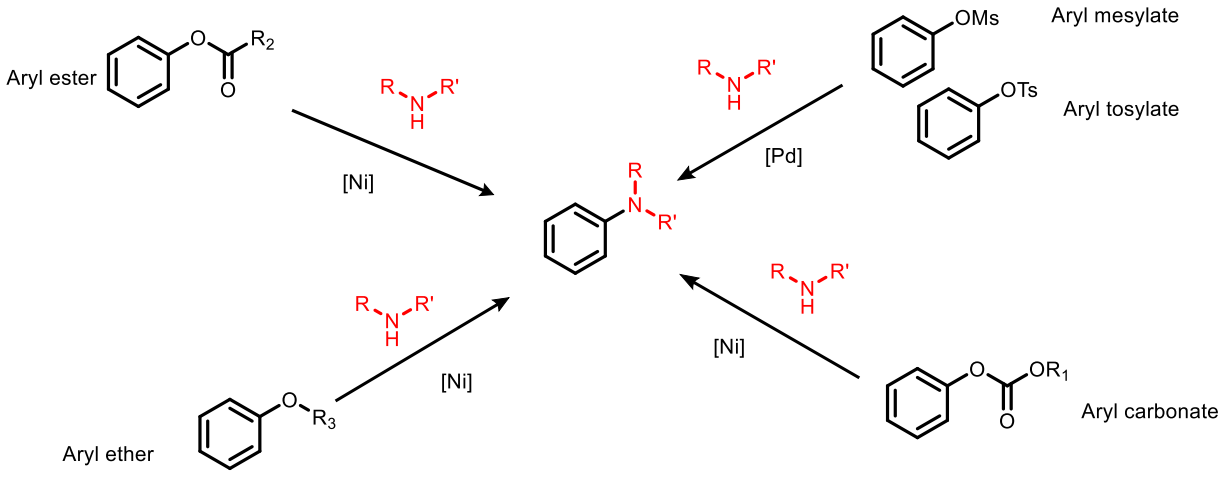


Figure 33 : Relative difficulty of C-O bond cleavage.[181]

Phenols could be a good alternative to replace aryl halides. Whereas, phenols are not widely engaged in direct cross coupling reactions as much as the aryls halides. Most of the phenol coupling reactions have been achieved after the transformation of hydroxyl group to another group such as sulfonate, ester, phosphate, ether…For example, the synthesis of aryl amines have been realized on different phenol derivatives like aryl sulfonate[182], carbonate[183], ester[184] and ether[185] by using transition metal catalyst systems, mainly with nickel and palladium (Scheme 118).



Scheme 118 : amination of phenol derivatives catalyzed by Ni and Pd.

In comparison, phenol direct amination is not widely studied. Consequently, the selective amination of phenols and derivatives remains an exciting challenge.

[181] H. Zeng, Z. Qiu, A. Dominguez-Huerta, Z. Hearne, Z. Chen, C-J. Li, *ACS. Catal.* **2017**, 7, 510.
[182] P. G. Alsabeh, M. Stradiotto, *Angew. Chem., Int. Ed*. **2013**, 52, 7242.
[183]T. Mesganaw, A. L. Silberstein, S.D. Ramgren, N. F. F. Nathel, X. Hong, P. Liu, N. K. Garg, *Chem. Sci.* **2011**, 2, 1766.
[184] E. Koch, R. Takise, A. Studer, J. Yamaguchi, K. Itami, *Chem. Commun*. **2015**, 51, 855.
[185] M. Tobisu, A. Yasutome, K. Yamakawa, T. Shimasaki, N. Chatani, *Tetrahedron* **2012**, 68, 5157.

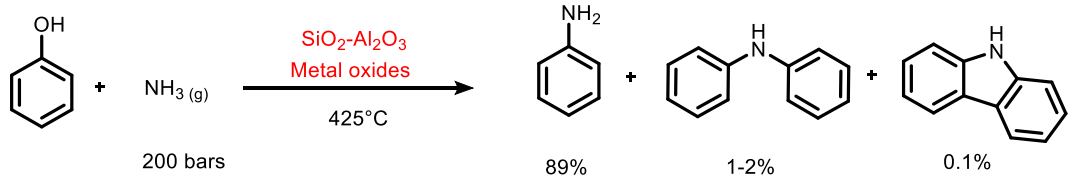
II. Direct amination of phenol

Herein, we report only the phenol amination works giving access to unprotected aniline and derivatives.

a. Phenol Amination in Gas Phase

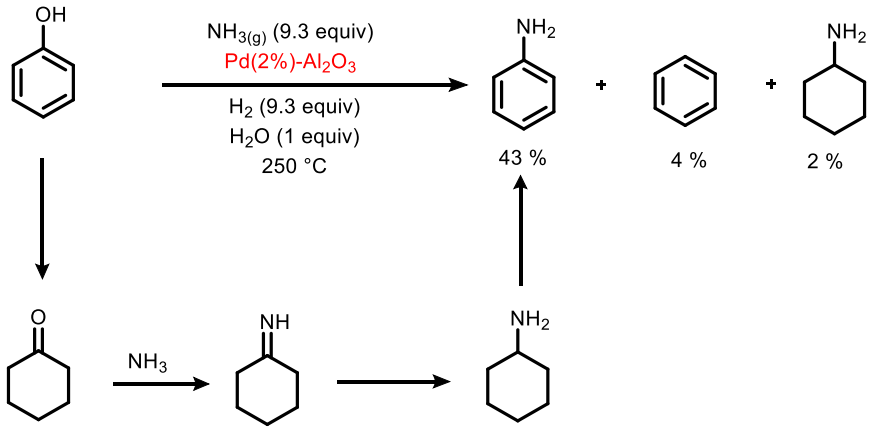
Phenol cross coupling reactions in gas phase have been developed first and foremost for the amination. These reactions have been done in flow reactors to manage and control the high pressure and high temperature.

In 1966, Halcon company patented the first phenol amination in gas phase in the presence of high concentrations of ammonia, metal oxide and Lewis acidic catalysts such as SiO_2-Al_2O_3, TiO_2-Al_2O_3…[186] The reaction is carried out at high temperatures (350 and 500°C) and high pressure (Scheme 119). The high reactivity in these conditions was conducted with the formation of diphenylamine and carbazole as byproducts.



Scheme 119 : amination of phenols using Lewis acidic catalysts in gas phase.

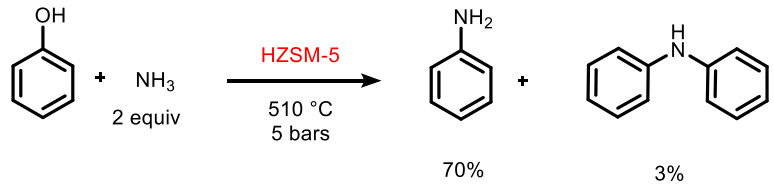
In 1981, Ono and Ishida described phenol amination with palladium supported on alumina as catalyst.[187] At 250 °C and in presence of hydrogen atmosphere, phenol molecule is converted to cyclohexanone, and then the ammonia attacks the ketone to yield 43 % of aniline after a dehydrogenation step (Scheme 120). Lower yields were obtained with other phenol derivatives due to the difficult hydrogenation step in the presence of substituents, for instance (*o*, *m* or *p*-) Cresol.



Scheme 120 : amination of phenol using Palladium supported on alumina.

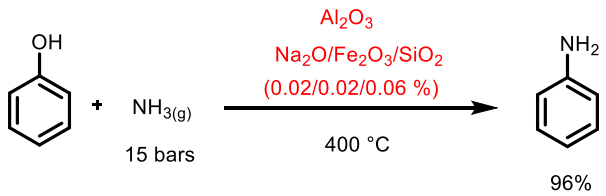
[186] R. S. Barker, Preparation of aminated benzenes from hydroxy benzenes. **1966**, US 3, 272, 865.
[187] Y. Ono, H. Ishida, *J. Catal.* **1981**, 72, 121.

Two years later, Chang and co-workers developed the amination of phenols at 510 °C with ZSM-5 a type of aluminosilicate zeolite with general formula $Na_nAl_nSi_{96-n}O_{192}\cdot 16H_2O$. This method gave aniline in high yield and 3% of diphenylamine as byproduct (Scheme 121).[188]



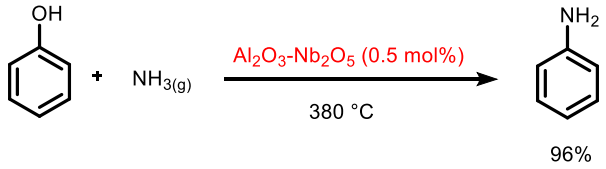
Scheme 121 : amination of phenol using zeolite.

In 1991, an acidic alumina catalyst was used at 400 °C for the amination of phenol (Scheme 122). The reaction showed a high conversion and a high aniline selectivity.[189] Noteworthy, the activity of the catalyst was maintained after 180 days of continuous process.



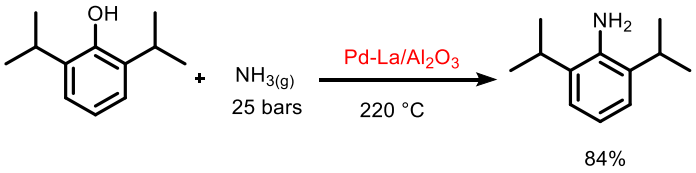
Scheme 122 : phenol amination catalyzed by acidic alumina.

At the same temperature, another catalyst based on niobium (Al_2O_3-Nb_2O_5) was engaged in the phenol amination to give the aniline in an excellent yield at 380 °C under high pressure (Scheme 123).[190] This work was patented by Washama's group in 1994.



Scheme 123 : phenol amination using niobium supported on alumina.

In 2005, Chen's group reported amination specifically for the 2,5-diisopropylphenol by using a mixture of palladium (0.5 %), Lanthanum (0.1 %) and Al_2O_3 (Scheme 124). This amination was carried out at high temperature 220 °C and high pressure of 25 bars.[191] The diisopropylaniline was obtained in 84% of yield.



Scheme 124 : synthesis of 2,5-diisopropylaniline.

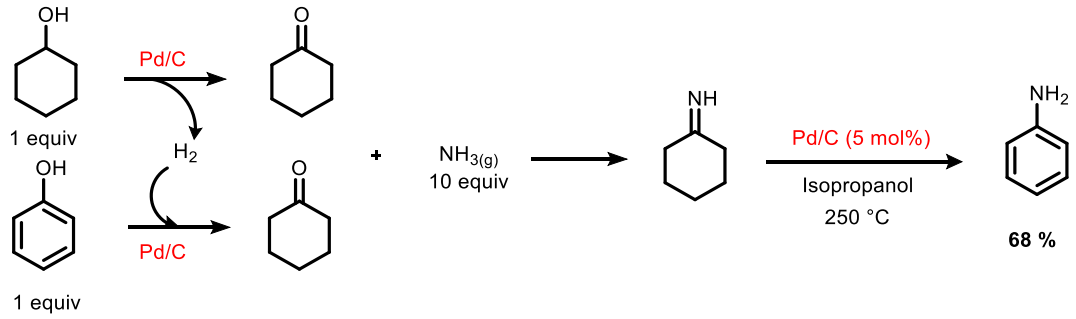
[188] C. D. Chang, W. H. Lang, Aniline or substituted aniline from phenol or phenolic compounds. **1982**, EP 6, 254, 2A1.
[189] M. Yasuhara, F. Matsunaga, Preparation of anilines. **1991**, US 4, 987, 260,
[190] Y. Mori, H. Noro, Y. Hara, T. Washama, Preparation of aromatic amines from phenols. **1994**, JP 06, 184, 062A.
[191] R. Jiang, Z. Xie, C. Zhang, Y. Yang, Q. Chen, *React. Kinet. Catal. Lett.* **2005**, 84, 215.

The last existing example so far for gas phase amination of phenol was patented in 2013. Using bentonite-based palladium catalysts, the reaction is carried out at lower temperature than the examples cited above.[192]

b. Phenols amination in liquid phase

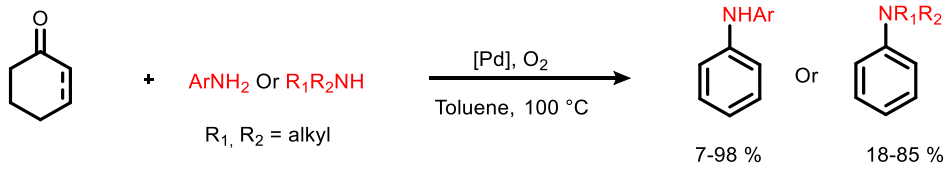
All the elaborated methods of the amination in gas phase require hard conditions, like high temperature and pressure and sometimes specialized equipment such as flow reactors besides the heterogeneous catalyst. These approaches are not compatible with a wide range of phenols derivatives and it is in most of the cases limited to the simplest one. So, the need of smoother conditions for phenol amination were studied and reported in literature.

Wakabayashi's group did the first phenol amination described in liquid phase on 1985.[193] The authors realized a simultaneous amination of phenol and cyclohexanol, where the latter serves as hydrogen transfer reagent. Later, the intermediate go through a dehydrogenation step over Pd/C to form the aniline. This method was limited on the simple phenol and requires high temperature as the example cited above (Scheme 125).



Scheme 125 : co-amination of phenol and cyclohexanol.

In 2012, Li's group developed a palladium catalytic system to realize the amination of cyclohexanone and cyclohexenone.[194] This reaction occurring by an amine condensation was followed by dehydrogenation step to afford aniline derivatives (Scheme 126). Under oxygen atmosphere, a wide scope of aniline derivatives with low to excellent yields has been developed at 100 °C.



Scheme 126 : palladium-catalyzed synthesis of aniline from cyclohexanone and cyclohexenone.

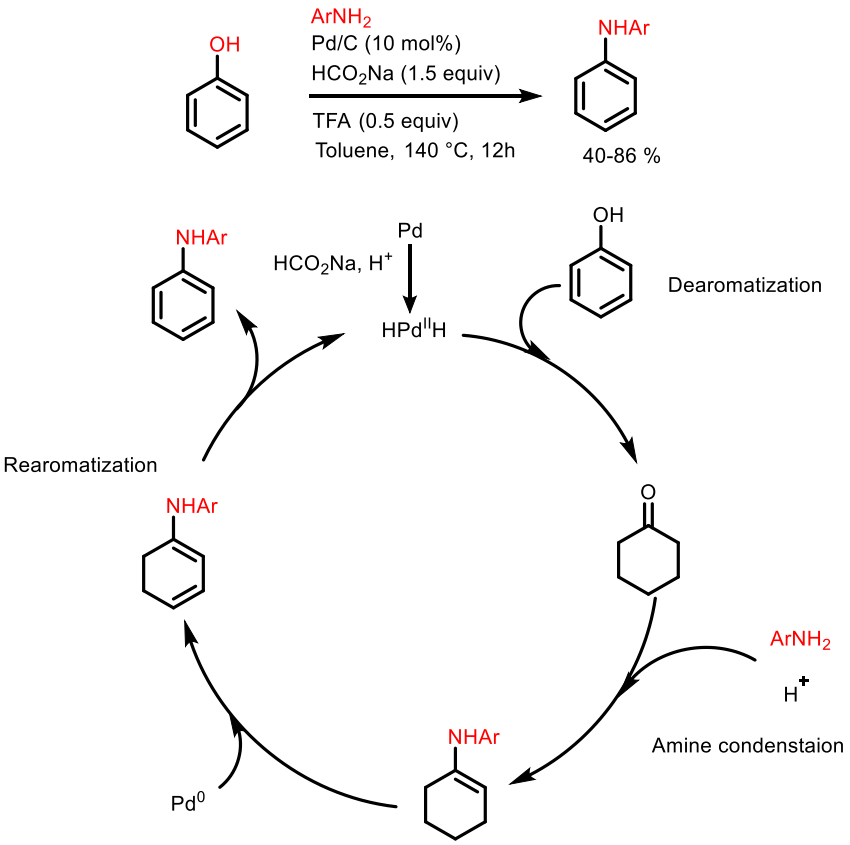
This concept was extensively studied later by the same group and developed directly on the phenol without any previous transformation on the aromatic ring. They used in 2015, sodium formate as hydride source in presence of palladium to generate *in situ* the cyclohexanone or cyclohexanone (Scheme 127). Both latter products can undergo a condensation with a secondary or primary amine to

[192] J. Ma, L. Wang, L. Chen, X. Dong, L. Wang, Bentonite-based amination reaction catalyst preparation method. **2013**, CN 1, 034, 183, 73A.

[193] H. Hamada, M. Yamamoto, Y. Kuwahara, T. Matsuzaki, K. Wakabayashi, *Bull. Chem. Soc. Jpn.* **1985**, 58, 1551.

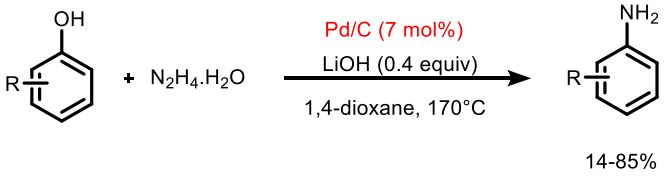
[194] S. A. Girard, X.Hu, T. Knauber, F. Zhou, M.-O. Simon, G.-J. Deng, C.-J. Li, *Org. Lett.* **2012**, 14, 5606.

afford selectively the corresponding *N*-substituted aniline after a rearomatization step.[195] Despite the high temperature that the method requires, it was applied on a large scope of phenol derivatives.



Scheme 127 : palladium-catalyzed amination of phenol.

Following their several works between 2012 and 2017 on the phenols amination,[181] Li's group recently developed the synthesis of aniline derivatives by using a palladium catalyzed reaction based on reductive dearomatization-condensation-rearomatization process.[196] The reaction is carried out in 1,4-dioxane at high temperature (170 °C) in the presence of LiOH in catalytic amount, and hydrazine as amine surrogate (Scheme 128). This reaction has been successfully applied on different phenol derivatives and in similar mechanism as the cited above. Traces of *N*-cyclohexylaniline and *N*-phenylaniline were formed as byproducts.

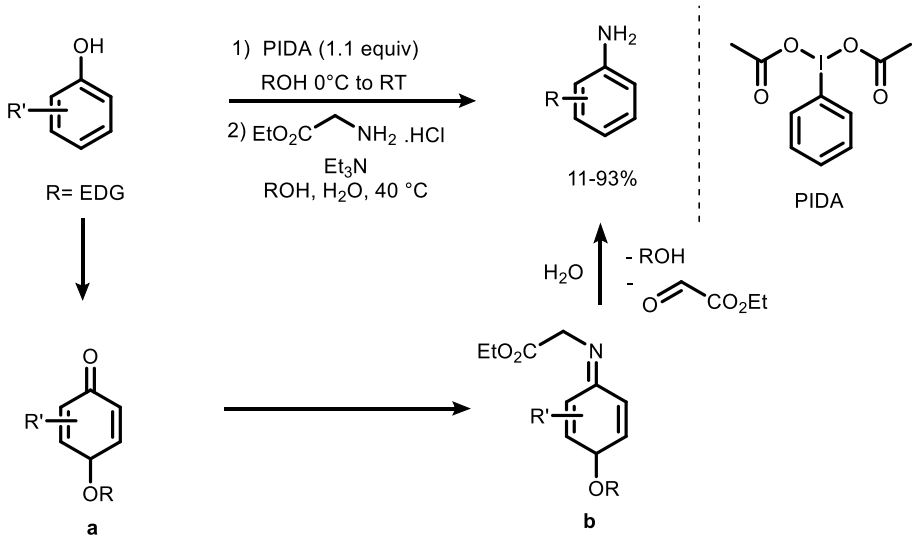


Scheme 128 : palladium-catalyzed direct amination of phenol.

In 2016, Alaniz's group described transition metal-free amination of phenols by using glycine ethyl ester as amine source. A stoichiometric amount of phenyliodine (III) diacetate (PIDA) have been used for the oxidative dearomatization to yield quinone monoketal **a** (Scheme 129). The latter undergoes a condensation with glycine and afford the corresponding imine **b**. Then, a hydrolysis step produce the

[195] Z. Chen, H. Zeng, S. A. Girard, F. Wang, N. Chen, C.-J. Li, *Angew. Chem. Int. Ed.* **2015**, 54, 14487.
[196] Z. Qiu, L. Lv, Jianbin Li, C.-C. Li, C.-J. Li, *Chem. Sci.*, **2019**, 10, 4775.

aniline derivatives in low to excellent yields. This method is limited to the electron rich phenols which is a drawback.[197]



Scheme 129 : metal free amination of electron rich phenols.

Despite the interest of aniline derivatives, the phenol direct amination is not widely studied to respond to the global need for the aniline moiety. All the existing methods require hard conditions such as high temperature, high pressure, specified equipment and/or expensive catalyst. These conditions limit the development of the methods on all the phenol derivatives. Therefore, the direct amination of phenol is still a challenge that needs many investigations. In this chapter, we investigated a new system for the phenol amination, in order to apply it for the modifications of phenols from biomass sources.

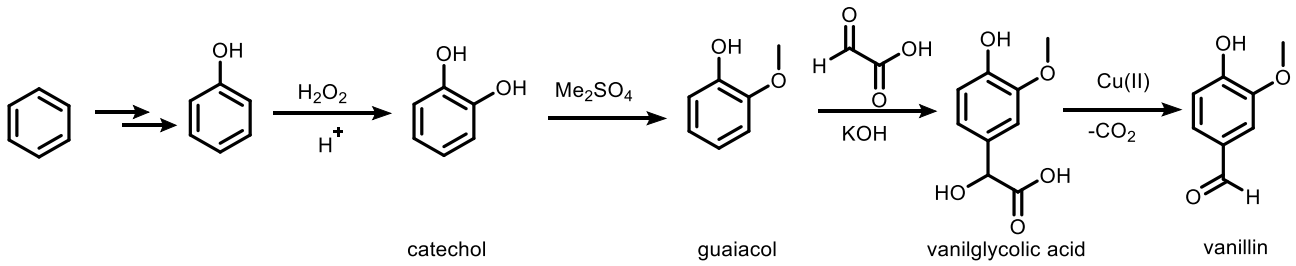
III. Preliminary tests and results

1. Goals

Biomass, known also as renewable resource, contains different families of phenols such as lignin, tannin, algae, cashew nut shell… These natural and non-toxic mono- and polyaromatic compounds are widely used in different fields like pharmaceutical, polymer and material chemistry.

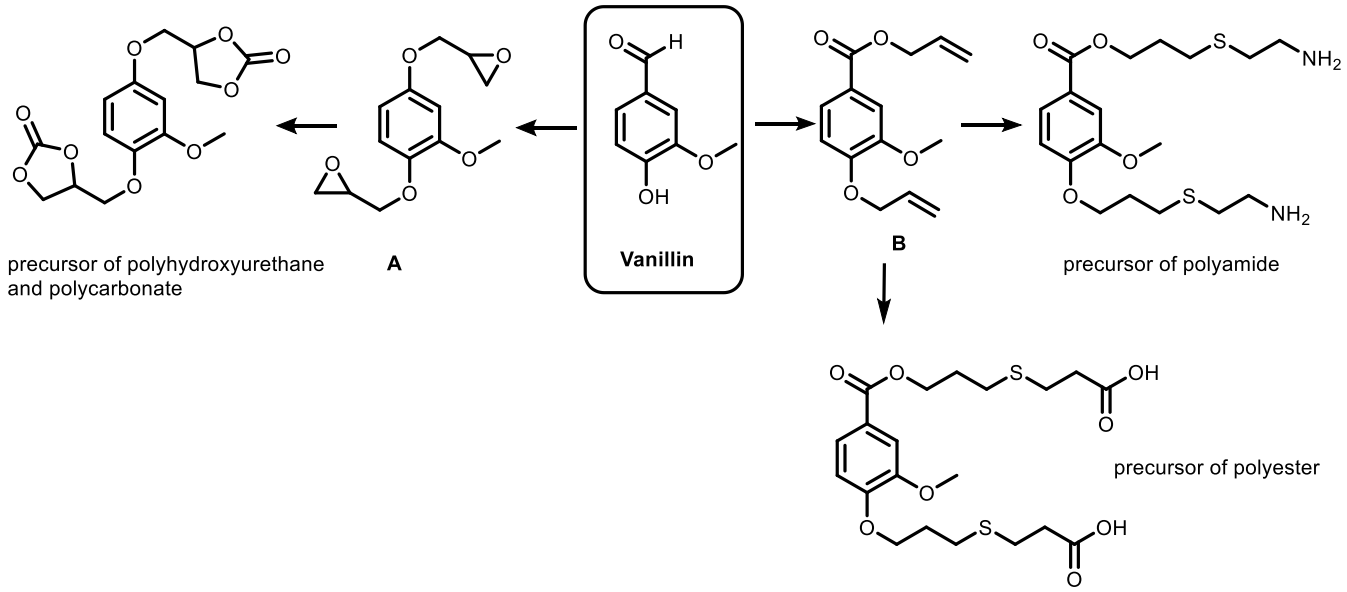
One of the most produced aromatics by the biomass is vanillin, which is extracted from the seedpods of Vanilla *planifolia.* Because of its high price and the increasing of the global need, vanillin is actually produced in a synthetic way as well.[198] Many synthesis were reported. For instance, phenol is obtained *via* benzene transformation, and converted to catechol by oxidation. A methylation step yield the guaiacol, which reacts with the oxacetic acid to yield the vanilglycolic acid that undergoes a decarboxylation step in presence of copper salts to yield the vanillin (Scheme 130).

[197] A. H. St. Amant, C. P. Frazier, B. Newmeyer, K. R. Fruehauf, J. Read de Alaniz. *Org. Biomol. Chem*., **2016**, 14, 5520.
[198] M. B. Hocking, *J. Chem. Educ.* **1997**, 74, 1055.



Scheme 130 : one of the methods for vanillin synthesis.

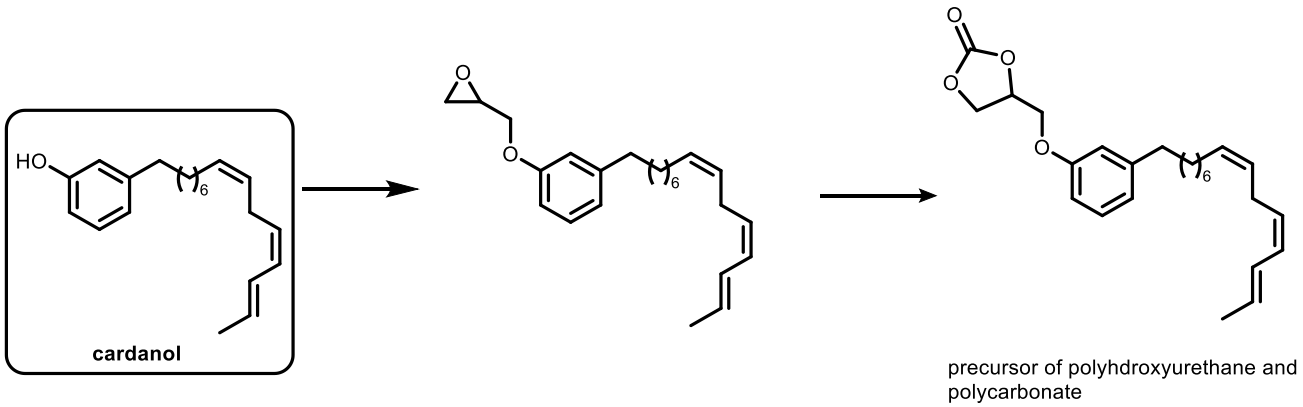
Vanillin contains two interesting functions: an aldehyde and a hydroxyl group. Both can undergo transformations to afford some interesting moieties serving later as monomers for the polymer synthesis (Scheme 131). For example, the resulted epoxy **A** is an interesting precursor for the polyhydroxyurethane and polycarbonate. While the allylic intermediate **B** can be transformed to many monomers, for the production of polyamides or polyesters.[199]



Scheme 131 : transformations of vanillin.

Another example of natural phenol is cardanol found in one of the cashew nut shell constituent. It contains two possible sites for functionalization, hydroxyl group and double bonds in the long chain substituting the aromatic ring on the *meta*-position. Many transformations have been applied to the cardanol to give access to valuable intermediate. For instance, an epoxy group can be grafted to yield a key intermediate for the polyhydroxyurethane and polycarbonate (Scheme 132).[200] Whereas, the olefin can undergo a metathesis to afford a new olefin.[201]

[199] M. Fache, E. Darroman, V. Besse, R. Auvergne, S. Caillol, B. Boutevin. *Green Chem.,* **2014**, 16, 1987.
[200] C. Voirin, S. Caillol, N. V. Sadavarte, B. V. Tawade, B. Boutevin, P. P. Wadgaonkar, *Polym. Chem.,* **2014**, 5, 3142.
[201] G. Vasapollo, G. Mele, R. Del Sole. *Molecules*, **2011**, 16, 6871.

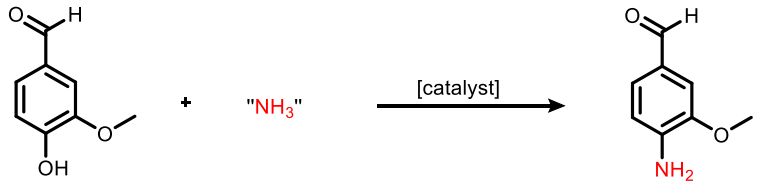


Scheme 132 : transformations of cardanol.

As previously mentioned, all these chemical transformations realized on vanillin and cardanol occurred by keeping the hydroxyl oxygen on the molecule. There is no example in the literature describing the total transformation of the hydroxyl to another group such as amine despite the high importance of the amine derivatives for post functionalization and diverse applications.

The functionalization of the carbon bearing the hydroxyl group by a nitrogen could yield interesting molecules with a wide possibility of applications mainly in the material field. The development of greener and more naturally abundant alternatives as aromatic raw materials is highly desirable. Due to their abundance, phenols are among the best candidates.

Therefore, in this project we are aiming to transform the phenol hydroxyl group to an amine without any previous transformation of –OH to another group. The key step of this substitution is to increase the dissociation energy of the C-O bond thereby facilitate the addition or the attack of a nucleophilic nitrogen atom. To overtake this challenge, a catalyst will be used (Scheme 133).



Scheme 133 : direct amination of vanillin.

In order to do direct amination in the *ipso*-position without any previous activation of the hydroxy group, we planned a simple way to increase the electrophilicity of the C-O bond, favorizing then a direct nucleophilic substitution.

In general, when a metal complexes an arene ring, the electrophilic character of the last one increases, the acidity of the arene's proton increases, which can facilitate many different processes like deprotonation, nucleophilic addition or substitution (Figure 34).[202]

[202] F. C. Piggie, J. J. Coniglio*, Curr. Org. Chem.* **2001**, 5, 757.

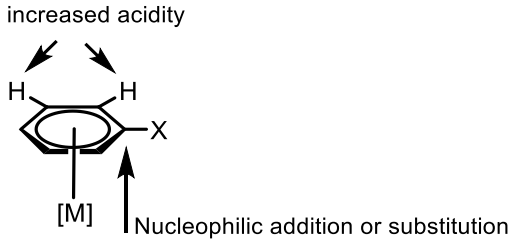
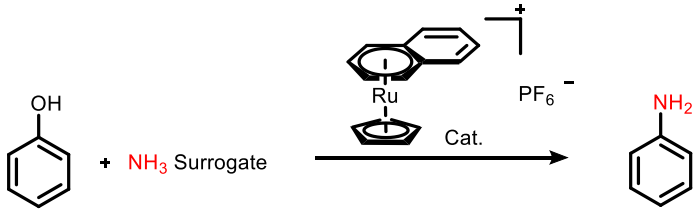


Figure 34 : the effects of a metal coordination to an arene.

Among the described η^6-arene complexes, the tricarbonyl chromium fragment ($Cr(CO)_3$) is the most studied. These electrophilic complex fragments have been applied widely for the arene transformations.[203] Since the pioneer discovery of these complexes, many other transition metals have been employed to form η^6-arene complexes, such as manganese, iron, ruthenium…

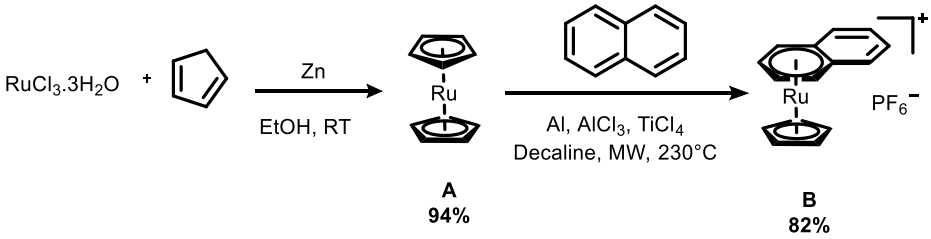
Based on these features for the metal-arene coordination, we planned to complex the phenol as model substrate to ruthenium, due to the robustness and the air-stability of the arene ruthenium complex.[204] Therefore, the electron density of the arene decreases, which could facilitate the nucleophilic substitution (Scheme 134).



Scheme 134 : direct amination of phenol via ruthenium π-complex.

2. Synthesis of starting materials and stoichiometric amination tests

To begin our study, we started with the synthesis of the ruthenium complexes. We were interested about the naphthalene complexes, which is labile due to the high haptotropic shift of naphthalene (from η^6 to η^4). So, the complex can undergo an easy exchange between the naphthalene and the phenol. Starting from the commercial Ruthenium (III) trichloride trihydrate and following described procedures[205], we synthesized ruthenocene by using freshly prepared cyclopentadiene cracked from its dimer. Ruthenocene is then subjected to an exchange with 1 equivalent of naphthalene in presence of aluminium powder, aluminium trichloride and titanium tetrachloride. This reaction is carried out in the microwave at 230°C to yield the ionic complexes $[CpRu(C_{10}H_8)]^+$ **B** (Scheme 135).



Scheme 135 : synthesis of $[CpRu(C_{10}H_8)]PF_6$ complex.

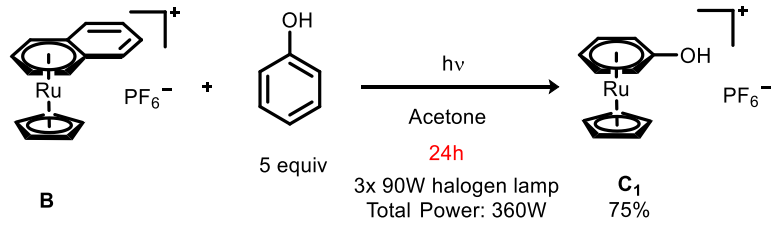
[203] A. R. Pape, K. P. Kaliappan, E. P. Kündig. *Chem. Rev*. **2000**, 100, 2917.
[204] E. P. Kündig, *Topics Organomet. Chem.* **2004**, 7, 3.
[205] E. P. Kündig, F. Monnier. *Adv. Synth. Catal*. **2004**, 346, 901.

The following step was the phenol naphthalene exchange. It can occur *via* two different activation modes: photochemical or thermal one.

- Photochemical arene exchange

In 2012, Kudinov and co-workers reported an arene-naphtalene exchange, starting from the same complex **B**.[206] Using high-pressure mercury vapor lamps (650 W) for the irradiation in acetone, they replaced the naphthalene by the simple phenol in 4-8 hours.

We applied this method, by using halogen lamps (360 W) and we got 75 % of the desired complex **C_1** after 24h (Scheme 136).



Scheme 136 : phenol-naphtalene exchange under photochemical conditions.

Using the same conditions, we tested the reactivity of diverse phenol derivatives to verify the electronic effect of the substitutions (Figure 35). We realized that the exchange is slower in the presence of EWG groups (i.e. **C_2** and **C_4**) comparing to the simple phenol. So, the reaction's rate is lower, which is requiring 60 hours for the total conversion of the starting complex. On the other hand, the reaction with 4-methoxyphenol, an electron rich phenol, gave the desired product **C_3** with total conversion of **B** in 24h. In all these tests, the conversion occurs with total selectivity.

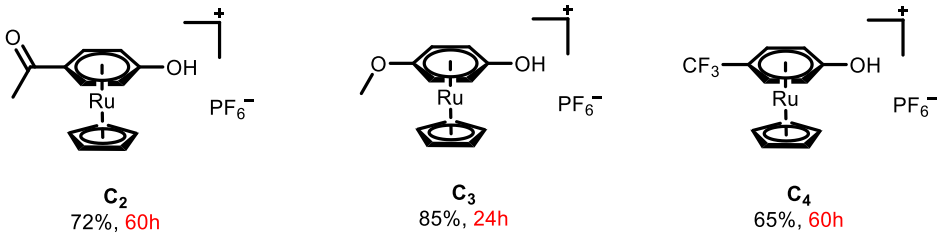
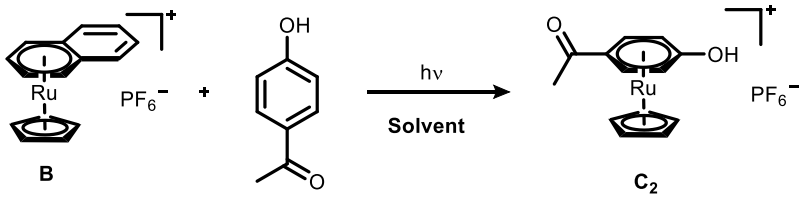


Figure 35 : yields of the phenol derivatives complexes.

In order to reduce the reaction time, different solvents have been tested with 4-hydroxyacetophenone (Table 31). With polar solvents like water, EtOH, or mixture of water and EtOH (to increase the solubility of the complex) the reaction was slow, affording 60% of conversion in 60 h in the best of the case (Entry 4). Whereas, with less polar solvents such as DCE and THF, there is no reaction and we recovered in the end the starting complex **B**.

[206] D. S. Perekalin,E. E. Karslyan, P. V. Petrovskii, A. O. Borissova, K. A. Lyssenko, A. R. Kudinov, *Eur. J. Inorg. Chem*. **2012**, 1485.

Table 31 : solvents tested in the photochemical conditions.



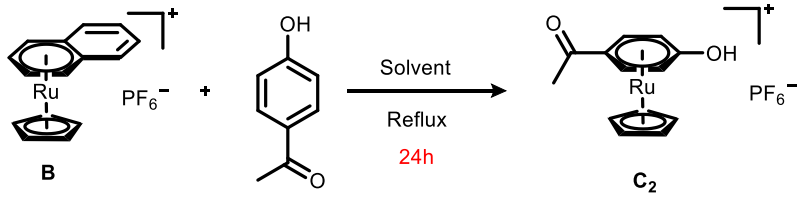
Entry	Solvent	Conversion (%)
1	Acetone	100
2	Water	10
3	EtOH	35
4	Water:EtOH	60
5	DCE	0
6	THF	0

To avoid this reactivity problem, we started to look for another alternative, and we tried to perform the reaction in thermal conditions.

- Thermal arene exchange

Using 4-hydroxyacetophenone as model substrate, we tried different solvents to find the best conditions (Table 32). Acetone and ethanol showed to be unsuitable for the thermal exchange (Entries 1-3). Under reflux of a mixture of dichloroethane and acetonitrile, we obtained a very good yield of **C_2** in 24h (Entry 4). 2 % of acetonitrile are necessary to release the naphthalene, due to a possible associative decomplexation. Indeed, the acetonitrile might works as additional coordinating ligand to stimulate the exchange between the two arenes.

Table 32 : product yields according to different solvent.



Entry	Solvent	Additive	Yield of C_2 (%)
1	Acetone	-	NR
2	EtOH	-	Traces
3	EtOH	ACN (2%)	17%
4	DCE	ACN (2%)	85%*
5	DCE	-	30%

*Yield corresponding to the product mass obtained after the reaction. In the other cases, Yield was measured comparing to B conversion, considering a selective reaction.

To validate the efficiency of these conditions, different phenols have been tested (Figure 36). With *m*-nitrophenol the exchange was slow, requiring 36h and affording after the work up only 43% of the complex **C_5** (B was not totally converted: yield was measured comparing to B conversion, considering a selective reaction). While after the reaction with 3,5-xylenol, we obtained **C_6** after 24h in a good yield (76%). The exchange of naphthalene with vanillin gave the desired complex **C_7** with excellent yield of 98%, proving the tolerance to many substituents with different electronic effect on the same aromatic ring.

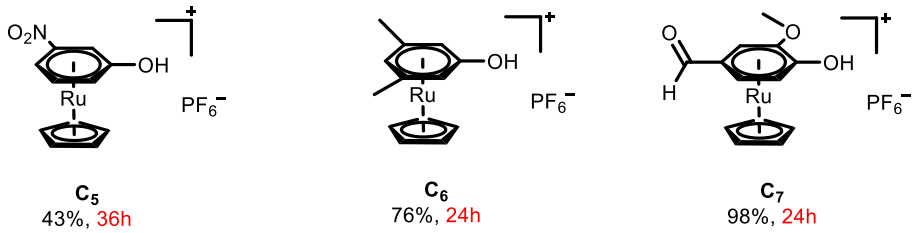
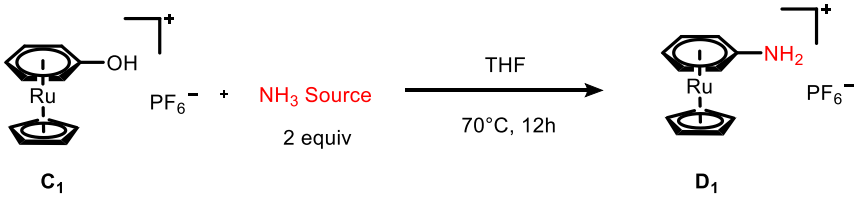


Figure 36 : naphthalene-Phenol exchange in thermal conditions.

In parallel, we started to engage the complexes (**C_x**) synthesized and cited above under amination conditions. We were looking to a simple source of amine, which can provide directly the unprotected aniline. Therefore, different commercial amine surrogates have been tested. We first chose THF as coordinating solvent and we started below the solvent's boiling point at 70°C (Table 33). Using 2 equiv of aqueous ammonia, any new product was observed, and we did not recover the starting complex (Entry 1). While under a gaseous ammonia stream, we recovered the starting material **C_1** and we did not get any new product (Entry 2). We supposed that the ammonia gas is not enough soluble in the THF, which could avoid any reaction.

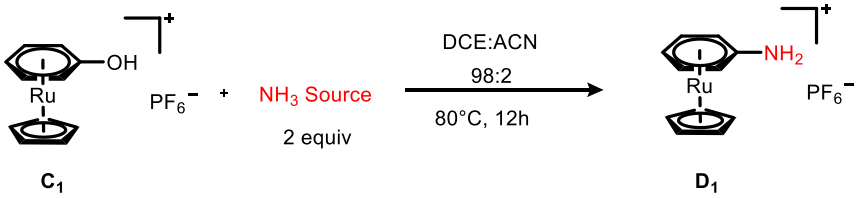
Table 33 : different amine sources tested in the reaction with THF as solvent.



Entry	Amine source	C1	D1
1	$NH_3.H_2O$	decomposed	-
2	NH_3 gaseous	recovered	-

For this reason, we changed the solvent and we tried DCE: ACN to be homogeneous with the exchange step (Table 34).

Table 34 : obtained results with different amine sources.



Entry	Amine source	C1	D1
1	$NH_3.H_2O$	decomposed	-
2	NH_3 gaseous	recovered	-
3	$LiNH_2$	deprotonated	-
4	NH_3.MeOH	deprotonated	-
5	NH_3.Dioxane	deprotonated	-
6	NH_4OAc	deprotonated	-

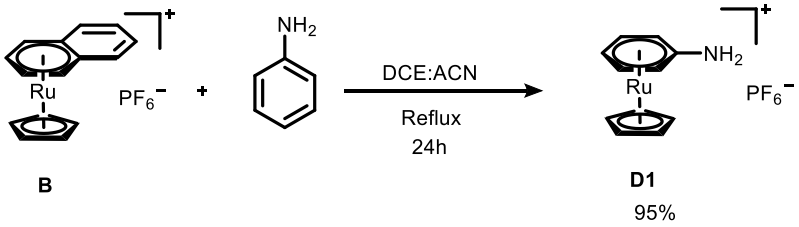
The result with aqueous and gaseous ammonia was the same in these new conditions (Entries 1-2). It is necessary to mention that we are following the reaction evolution by the proton signal of the cyclopentadiene moiety, which is a singlet of 5 protons (5.43 ppm for the starting complex **C1**). The reaction with 2 equiv of lithium amide, afforded a new product with a total conversion of the starting

one. Based on the HRMS and IR analysis we supposed that the product is the η^5-Oxocyclohexadienyl resulting from the deprotonation of the hydroxyl group. To be sure of its identity, we protonated the resulting product with HPF_6, and we obtained by NMR confirmation the phenol complex **C1** (Scheme 137).

Scheme 137 : protonation of η^5-Oxocyclohexadienyl.

Using NH_3 in MeOH, in dioxane or NH_4OAc (Table 34, entries 4-6) the starting complexes disappeared completely from the NMR spectra and we obtained, a new and different product for each reaction. As we are not able to identify the products by NMR, and we were not able to recrystallize them, we though that a high-resolution mass analysis can help us to discover these three new products. We were surprised by the results: the three new products have the same mass corresponding to a deprotonated phenol complex.

To have a reference mainly in NMR, we did the direct exchange between naphthalene and aniline. The corresponding complex **D1** was obtained in excellent yield after 24h of reflux in a mixture of DCE and acetonitrile (Scheme 138). The corresponding Mass and NMR spectra have been used to follow our reactions results.



Scheme 138 : synthesis of η^6-aniline ruthenium complex.

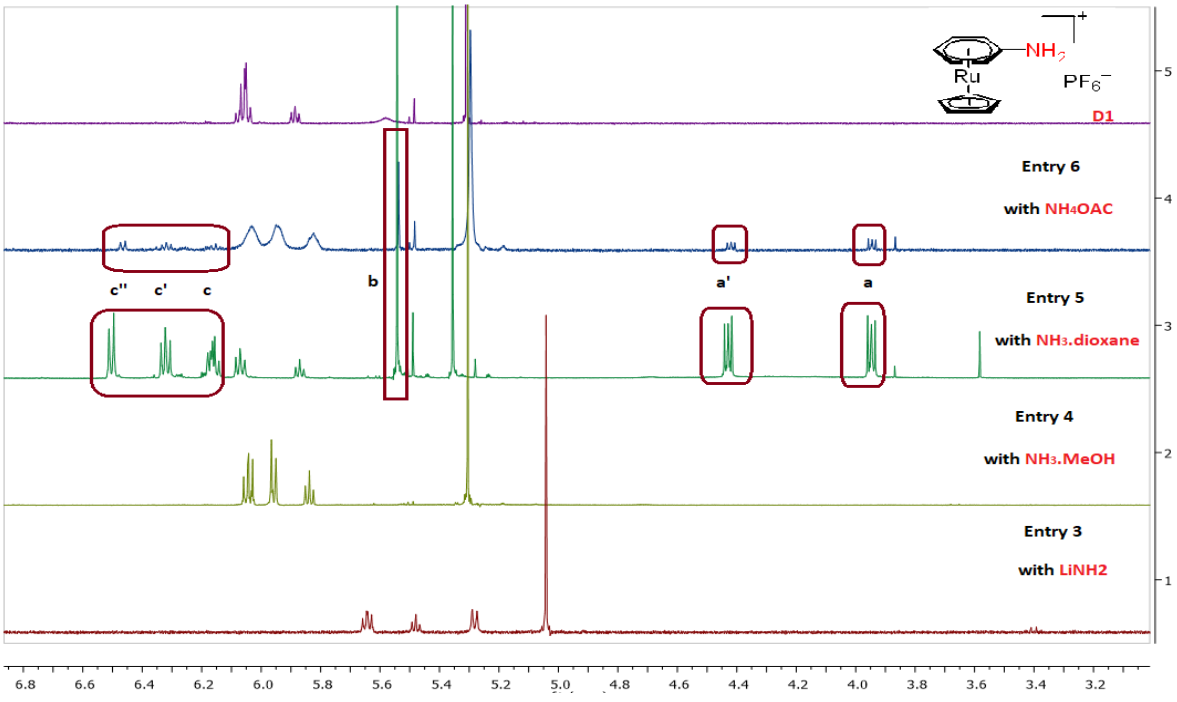


Figure 37 : Comparison of NMR spectras.

Meanwhile, the appearance of a second product in the NMR spectra of entries 5 and 6 took our attention (Figure 37). When we used NH_3 in dioxane or NH_4OAc as amine source, we observed the formation of a common product having two proton signals **a** and **a'** in the dishielded aliphatic zone (Figure 38). These signals are accompanied with a singlet **b** at 5.54 ppm and some pics in the aromatic zone **c**, **c'** and **c"**.

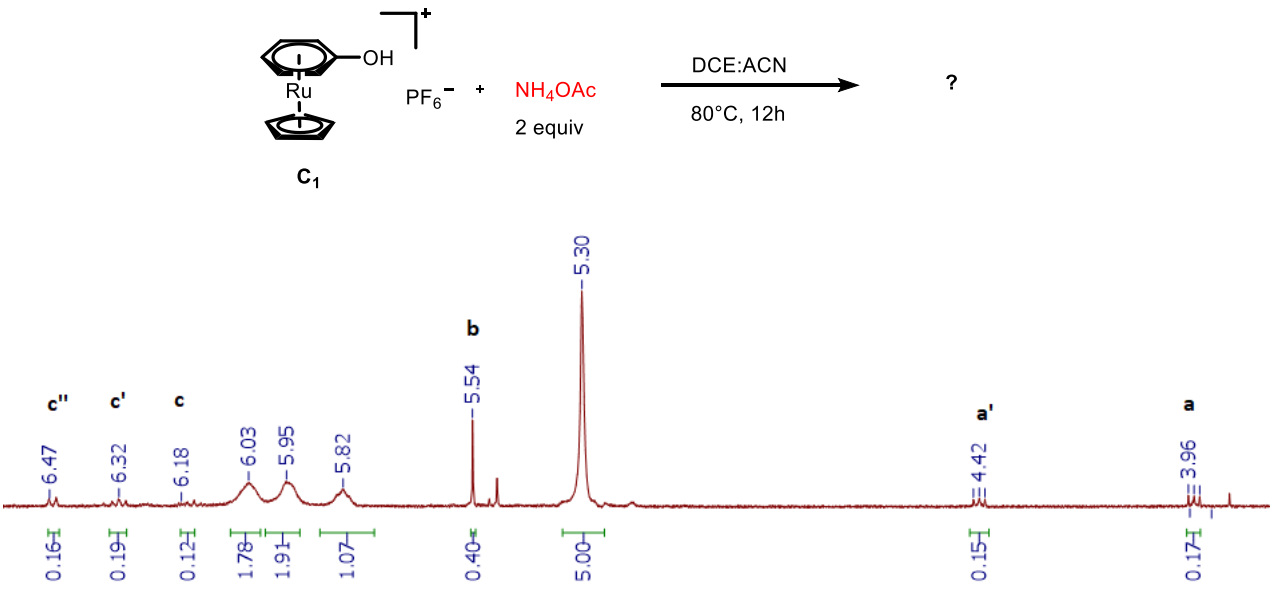


Figure 38 : NMR spectra for the amination reaction with NH_4OAc in DCE.

The ratio between the pics **a**, **a'**, **b**, **c**, **c'** and **c"** is respectively 2: 2: 5: 1: 2 and 2 confirming the presence of cyclopentadiene moiety, and a monosubstituted benzene. We supposed that the suspecting signals **a** and **a'** may refer to the reacting dichloroethane with the arene complex, as they both appear as triplet. So, we proposed different complexes that can be formed by the reaction of phenol or aniline with DCE (Figure 39). The complexes **1** and **2** could result from a mono nucleophilic

substitution of the oxygen and the nitrogen respectively with a chlorine atom. Whereas, complex **3** may result from double nucleophilic substitution with the two chlorine atoms.

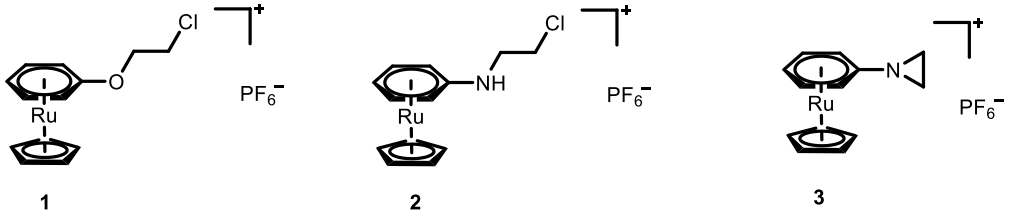
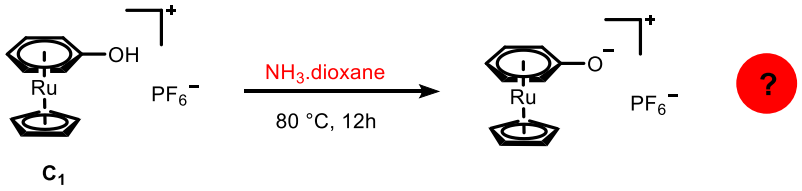


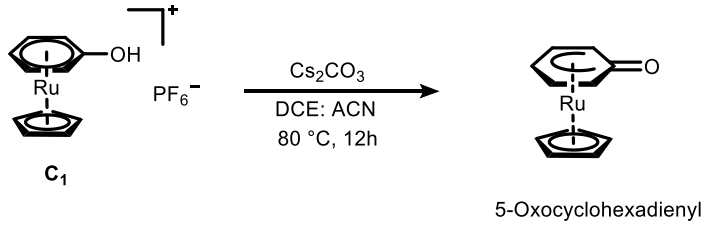
Figure 39 : proposed structure for the byproduct.

To verify our hypothesis, we performed different tests. First, we started by removing DCE from the reaction. We realized the reaction in NH_3.dioxane as solvent and reagent in the same time. We did not observe the unknown product, and we got a similar chemical shift as the complex **D_1.** Contrary, the HRMS result is quite similar for the deprotonated phenol and does not contain nitrogen atom (Scheme 139). This test serves as confirmation that the DCE plays a role in the formation of the unknown product.



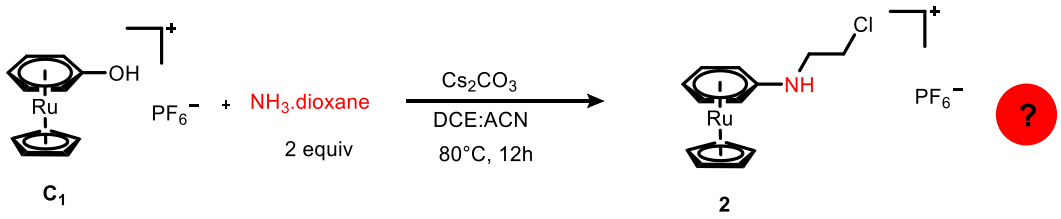
Scheme 139 : reaction in NH_3.dioxane as solvent.

Another significant test was carried out. The aim was to see if the presence of a base can influence the formation of the unknown product. We replaced the NH_3.dioxane by 1 equiv of cesium carbonate, to see if the deprotonated phenol is able to do a nucleophilic substitution with chlorine atom of DCE. The reaction yields only the η^5-Oxocyclohexadienyl excluding the possibility of the formation of **1** (Scheme 140).



Scheme 140 : deprotonation of phenol complex in DCE.

On the other hand, after the reaction in presence of both NH_3.dioxane and Cs_2CO_3 (Scheme 141), **C_1** was totally converted to form selectively the unknown product. The corresponding mass analysis confirmed the presence of chlorine atom and refer mostly to the complex **2**. We are planning many tests to confirm this result and to identify the nature of this product.



C1 2

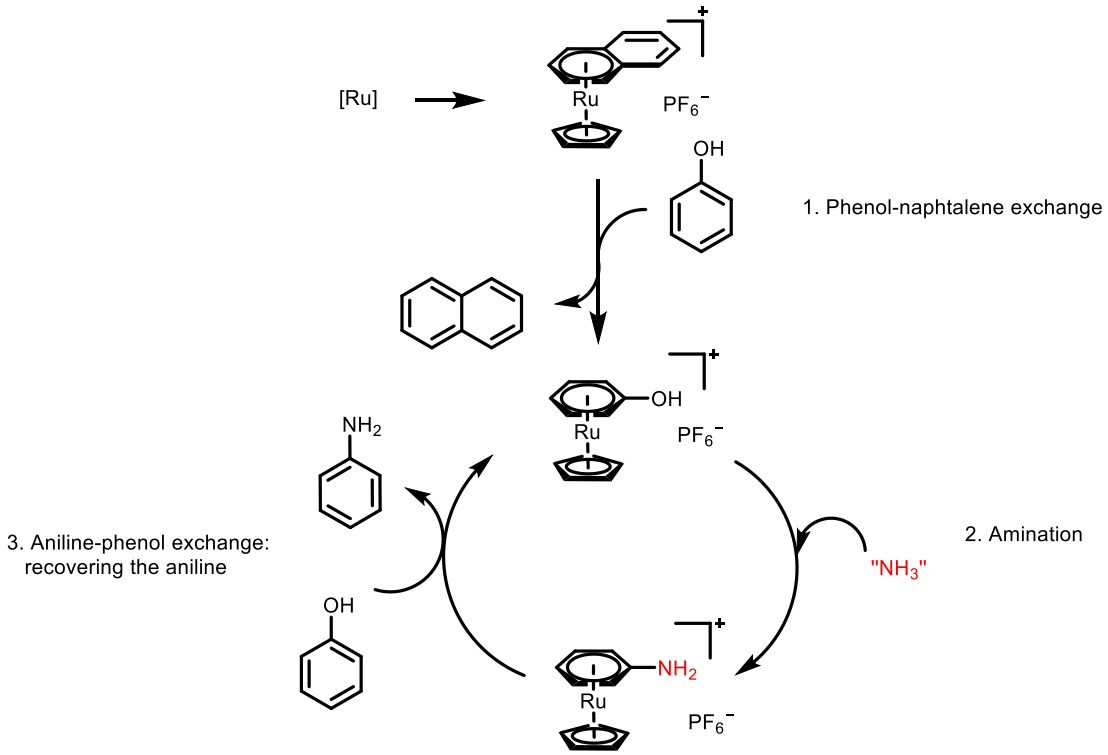
Scheme 141 : reaction of phenol complex with NH_3.dioxane in presence of a base.

It is worthy to note, that we tried to analyze the complexes by ^{15}N NMR, but we were not able to detect any signal, it might that the ruthenium is disturbing the analysis or it is due to the absence of the nitrogen atom.

At the moment of writing this chapter, the work is not finished yet. This project is going to be continued in our laboratory to realize the phenol amination in catalytic conditions.

3. Conclusion and perspectives

To conclude, we planned to find an original system for the direct amination of phenol without any previous transformation or activation of the hydroxyl group. Currently, we are working to find suitable conditions in stoechiometric manner. Therfeore, the next step will be the application of this method in catalytic route (Scheme 142). In case of succes, this system could be applied later on the phenols from biosources origin to afford valuable aniline derivatives that can be useful for many post transformations mainly in polymer field.



Scheme 142 : planned pathway for the Ru-catalyzed direct amination of phenol.

IV. Experimental part

General considerations

All reactions were performed in oven-dried Schlenk flasks under an atmosphere of argon closed with Rodavis® Screw caps or in microwave tubes. Ruthenium trichloride, *trans*-decaline, and phenol derivatives were purchased from Sigma-Aldrich® and Alfa Aesar®. They are used as received. Ruthenium trichloride is stored in a desiccator cabinet and weighed to air. Amine surrogates were purchased from Sigma-Aldrich® and Fluorochem and used as received. Dicyclopentadiene was purchased from Alfa Aeser and used freshly after cracking. Other reagents were purchased from either Sigma-Aldrich® or Alfa Aesar® or Acros Organics® and used as received.

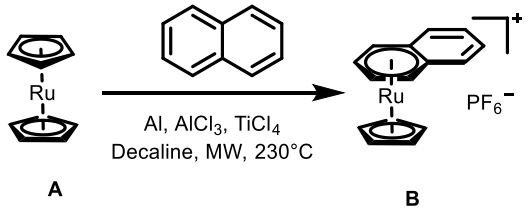
^{1}H and ^{13}C NMR spectra were recorded with a Bruker AC-400 MHz spectrometer in $CDCl_3$. For ^{1}H NMR (400 MHz), acetone served as internal standard (δ = 2.05 ppm) and data are reported as follows: chemical shift (in ppm), multiplicity (s = singlet, bs = broad singlet, d = doublet, t = triplet, q = quartet, dd = doublet of doublets, dt = doublet of triplets, td = triplet of doublets, ddd = doublet of doublet of doublets, m = multiplet), coupling constant (in Hz), and integration. For ^{13}C NMR (100 MHz), acetone served as internal standard (δ = 29.84 and 206.26 ppm) and spectra were obtained with complete proton decoupling. Gas chromatography–mass spectra (GC-MS) were recorded on a Shimadzu QP2012-SE with a Zebron ZB-5MS (20m × 0,18mm), capillary apolar column (Stationary phase: 0.18 µm film). GC-MS method: Initial temperature: 50°C; Initial time: 2 min; Ramp: 22°C/min; Final Temperature: 280°C; Final time: 15min or 23min. GC-MS was used only for the analysis of the naphthalene and the free phenol derivatives after the exchange step. HRMS (Q-TOF) were performed on a JEOL JMS-DX300 spectrometer (3 keV, xenon) in a m-nitrobenzyl alcohol matrix.

Procedure for the synthesis of ruthenocene A

A Schlenk tube (200 mL) equipped with a magnetic stirring bar was charged with ruthenium trichloride (5.26 g, 0.02 mol) and freshly distilled ethanol (80 mL). Freshly cracked cyclopentadiene (25 mL, 0.3 mol) was added to the dark red-black solution followed by zinc dust (13 g, 0.2 mol, added in 5 portions). The reaction mixture turned rapidly dark blue, and later to dark grey. After stirring for 2.5 hours at room temperature, the mixture was filtered on a celite pad. The solid was washed with toluene (15 mL) for 4 times and the filtrate was evaporated to dryness. The solid residue was then solubilized in toluene (500 mL) and passed through a plug of silica gel and washed again with toluene. The resulting solution was evaporated to dried to afford the ruthenocene **A** as white crystalline solid (4.3 g, 96%).

^{1}H NMR (400 MHz, CDCl3) δ 4.59 (s, 5H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 70.1.

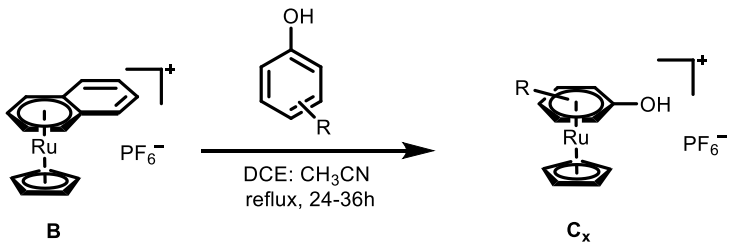
Procedure for the synthesis of the complex B



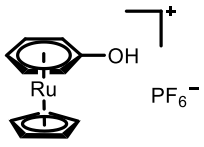
To a 20 mL microwave vial equipped with a magnetic stirring bar were added: ruthenocene (2.31 g, 10 mmol), naphthalene (2.56 g, 20 mmol, 2.0 eq), Al (fine powder added carrefuly, 135 mg, 5 mmol, 0.5 equiv), and $AlCl_3$ (2.70 g, 20 mmol, 2.0 eq). Then the vial was sealed, degassed, and purged with N_2. Degassed decaline (15 mL) was added. The mixture was stirred for 5 min., then $TiCl_4$ (550 µL, 5 mmol, 0.5 equiv) was added. The mixture was stirred for 5 min. before being subjected to microwave irradiation for 15 min. at 230 °C (pre-stirring 30 sec., normal absorption level). After cooling to rt, the reaction mixture was poured into a mixture of ice and water (80 mL), 32% HCl (20 mL), 30% H_2O_2 (20 mL) and stirred vigorously for 10 min. The resulting orange solution was extracted with pentane (3 × 200 mL) and the aqueous phase **1** was kept. The combined organic phases were extracted with water (2 × 100 mL) and the aqueous phase **2** was recovered. To the combined aqueous phases (**1** and **2**) was added KPF_6 (2.76 g, 15 mmol, 1.5 eq.) to give a yellow precipitate and the resulting mixture was stirred for 10 min. The aqueous solution was extracted with CH_2Cl_2 (4 × 200 mL), and then the combined organic phases were dried over $MgSO_4$, filtered, concentrated under vacuum to afford an orange solid. The crude product was dissolved in 60 ml of CH_2Cl_2 and filtered through a short plug of celite (4 x 5 cm). The celite was washed with CH_2Cl_2 until washings become colorless. The CH_2Cl_2 solution was concentrated to and then poured into vigorously stirred diethyl ether (100 mL) to yield an off-white colored precipitate which was filtered and washed with pentane (3 × 20 mL). The light cream-colored solid was dried in air and stored in a flask packed by aluminium foil (3.5 g, 82%).

^{1} H NMR (400 MHz, acetone-d6): δ 5.15 (s, 5H), 6.47-6.48 (m, 2H), 7.24-725 (m, 2H), 7.70-7.73 (m, 2H), 7.89-7.92 (m, 2H). ^{13}C NMR (100 MHz, acetone-d6): 79.7, 83.9, 85.9, 97.2, 129.3, 131.5. ^{31}P NMR (162 MHz, acetone-d6): δ -144.1.

General procedure for thermal exchange between naphthalene and phenol derivatives

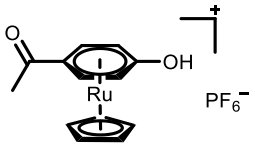


After standard cycles of evacuation and back-filling with argon, an oven-dried Schlenk flask equipped with a magnetic stirring bar was charged with complex **B** (44 mg, 0.1 mmol) and phenol derivative (1 mmol, 10 equiv) in 1,2-dichloroethane (5 mL) and MeCN (0.1 ml). Then the mixture was heated to reflux for the indicated time (24-36h). After allowing the reaction to cool to room temperature, the solvent was evaporated, and the residue was washed several times with Et_2O to remove unreacted phenol and liberated naphthalene. The solid was purified **C** by trituration with Et_2O.

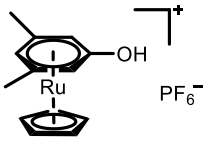


C1

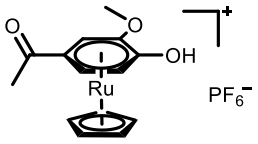
The reaction of phenol (1 mmol, 94 mg) according to the general procedure gave the complex **C_1** in the form of beige solid (75 %, 30 mg).
^{1}H NMR (400 MHz, Acetone) δ 6.30 (d, *J* = 5.9 Hz, 2H), 6.24 – 6.17 (m, 2H), 6.01 (t, *J* = 5.3 Hz, 1H), 5.43 (s, 5H). ^{13}C NMR (101 MHz, Acetone) δ 85.34, 83.11, 80.70, 76.32.
^{31}P NMR (162 MHz, Acetone) δ -144.27.



The reaction of 4-hydroxyacetophenone (1 mmol, 136 mg) according to the general procedure gave the compex **C_2** in the form of grey solid (85 %, 39 mg).
^{1}H NMR (400 MHz, Acetone) δ 6.78 (d, *J* = 6.7 Hz, 2H), 6.51 (d, *J* = 6.7 Hz, 2H), 5.53 (s, 5H), 2.61 (s, 3H).
^{31}P NMR (162 MHz, Acetone) δ -144.01.



The reaction of 3,5-xylenol (1 mmol, 122 mg) according to the general procedure with 24h at reflux gave the compex **C_6** in the form of black solid (76 %, 34 mg).
^{1}H NMR (400 MHz, Acetone) δ 6.20 (s, 2H), 5.95 (s, 1H), 5.29 (s, 5H), 2.35 (s, 6H).
^{31}P NMR (162 MHz, Acetone) δ -144.45.

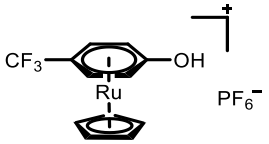


The reaction of vanillin (1 mmol, 152 mg) according to the general procedure with 24h at reflux gave the compex **C_7** in the form of brown solid (98 %, 47 mg).
^{1}H NMR (400 MHz, Acetone) δ 6.55 (s, 1H), 6.35 (d, *J* = 6.8 Hz,1H), 5.95 (d, *J* = 6.8 Hz,1H), 5.29 (s, 5H), 2.59 (s, 3H), 2.35 (s, 6H). ^{31}P NMR (162 MHz, Acetone) δ -144.44.

General procedure for photochemical exchange between naphthalene and phenol derivatives

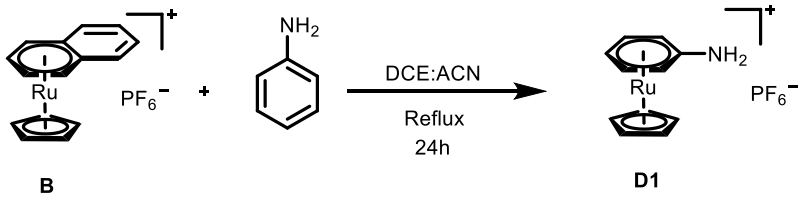
After standard cycles of evacuation and back-filling with argon, an oven-dried Schlenk flask equipped with a magnetic stirring bar was charged with complex **B** (44 mg, 0.1 mmol) and phenol derivative (1

mmol, 10 equiv) in freshly distilled acetone (5 ml), then the mixture was subjected to irradiation by three halogen lamps (3x90W) for the indicated time (24-60h). The solvent was evaporated, and the residue was washed several times with Et_2O to remove unreacted phenol and free released naphthalene. The solid was purified **C** by trituration with Et_2O.



The reaction of 4-trifluoromethylphenol (1 mmol, 162 mg) according to the general procedure gave the compex **C_4** in the form of black solid (65 %, 31 mg).
^{1}H NMR (400 MHz, Acetone) δ 6.55 (d, *J* = 6.9 Hz, 2H), 6.35 (d, *J* = 6.9 Hz, 2H), 5.52 (s, 5H).
^{31}P NMR (162 MHz, Acetone) δ -144.42.

Procedure for thermal exchange between naphthalene and aniline

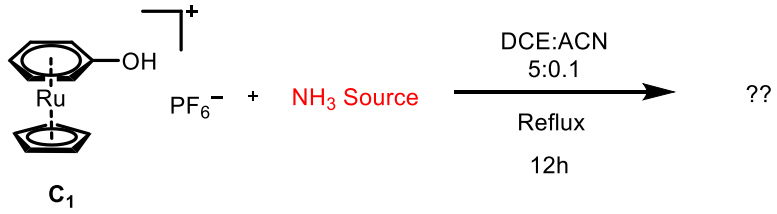


B **D1**

After standard cycles of evacuation and back-filling with argon, an oven-dried Schlenk flask equipped with a magnetic stirring bar was charged with complex **B** (44 mg, 0.1 mmol) and aniline (1 mmol, 93 mg) in 1,2-dichloroethane (5 ml) and MeCN (0.1 ml) was heated to reflux for 24h. After allowing the reaction to cool to room temperature, the solvent was evaporated, and the residue was washed several times with Et_2O to remove unreacted phenol and free realeased naphthalene. After, a trituration with Et_2O afford **D_1** in form of white solid (95%, 37 mg).

^{1}H NMR (400 MHz, Acetone) δ 6.11 – 6.02 (m, 4H), 5.91 – 5.85 (m, 1H), 5.59 (bs, 2H), 5.31 (s, 5H).
^{13}C NMR (101 MHz, Acetone) δ 84.86, 81.17, 79.92, 71.47. ^{31}P NMR (162 MHz, Acetone) δ -144.26.

Procedure for the reaction of phenol complexes with amine surrogate



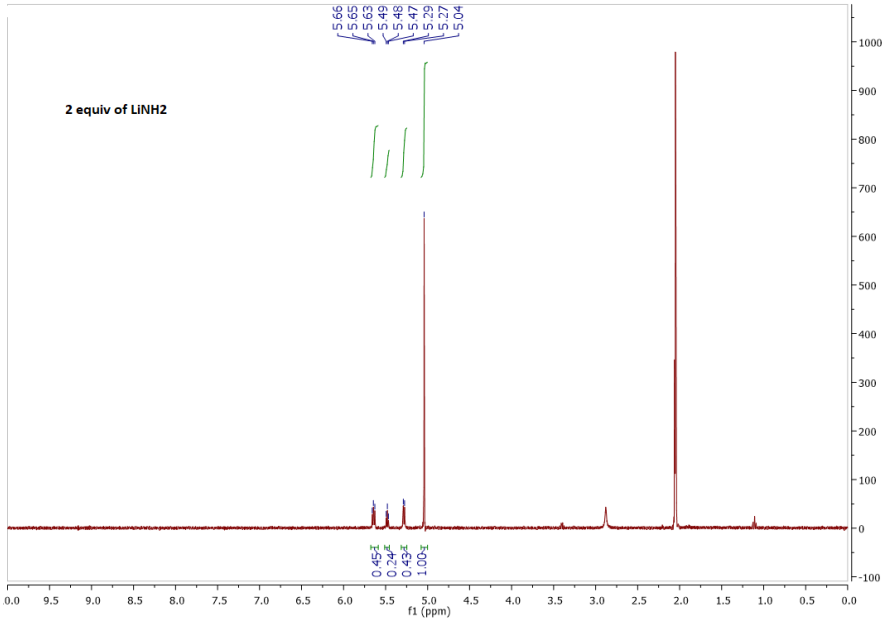
C_1

After standard cycles of evacuation and back-filling with argon, an oven-dried Schlenk flask equipped with a magnetic stirring bar was charged with the amine source (0.2 mmol, 2 equiv), and the phenol complex **C_1** (40 mg, 0.1 mmol) . If the amine source is solid, the tube was evacuated and back-filled with argon. And this procedure was repeated three times. Under a stream of argon, 5 ml of dry CH_2Cl_2

were and added, followed by the addition of 0.1 ml of dry acetonitrile. The Schlenk is sealed under a positive pressure of argon, stirred under reflux for 12h. After allowing the reaction to cool to room temperature, the solvent was evaporated and the residue was dissolved in acetone and filtered through a short plug of celite and washed with acetone. The solution was evaporated to afford the new complex.

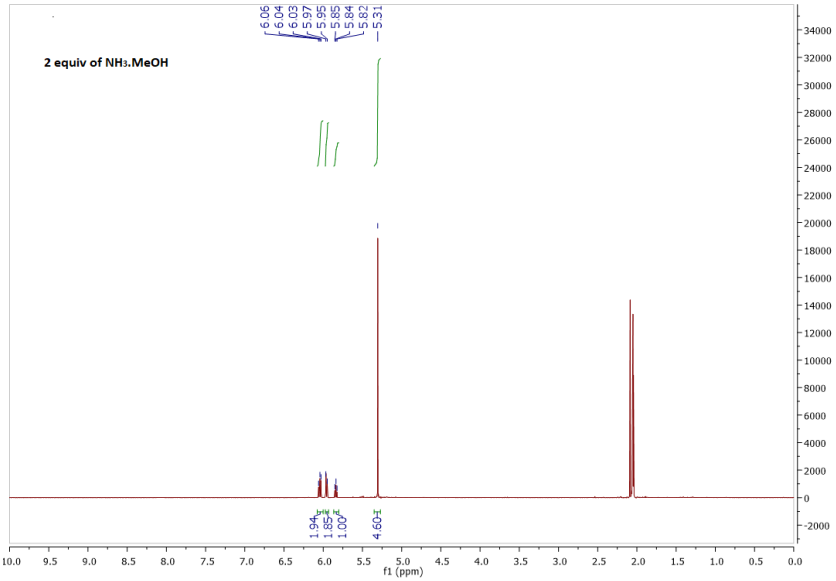
- $LiNH_2$ (5 mg, 2 equiv):

^{1}H NMR (400 MHz, Acetone) δ 5.67 – 5.62 (m, 2H), 5.48 (t, *J* = 5.1 Hz, 1H), 5.28 (d, *J* = 6.3 Hz, 2H), 5.04 (s, 5H).
^{31}P NMR (162 MHz, Acetone) δ -144.30.



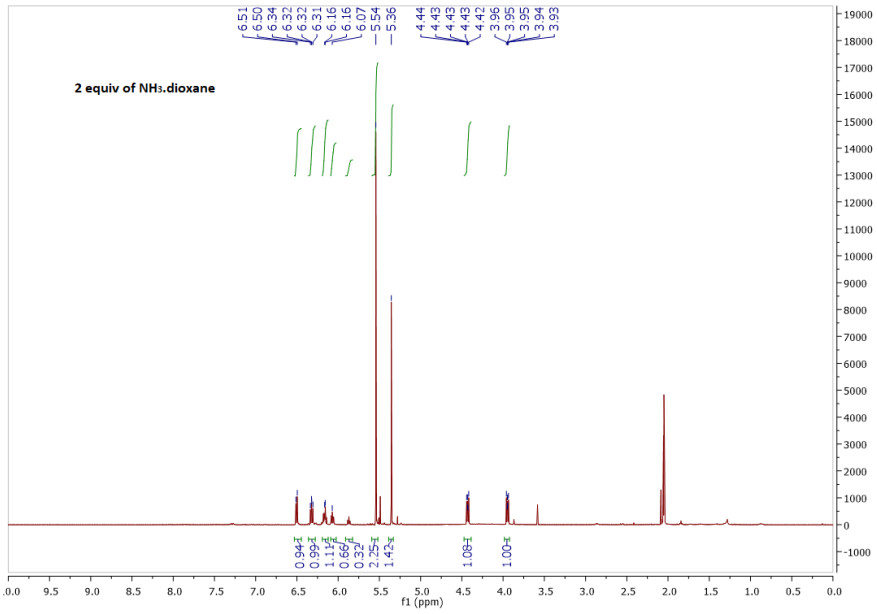
- NH_3 in MeOH (3µl, 2 equiv):

^{1}H NMR (400 MHz, Acetone) δ 6.07 – 6.02 (m, 2H), 5.96 (d, *J* = 7.3 Hz, 2H), 5.84 (t, *J* = 5.1 Hz, 1H), 5.31 (s, 5H).
^{31}P NMR (162 MHz, Acetone) δ -144.25.



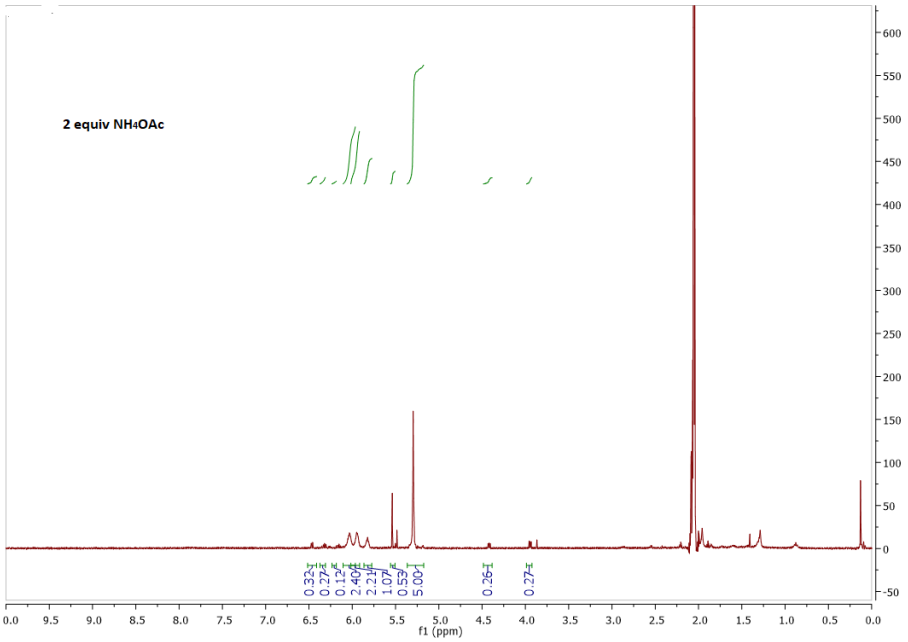
- NH_3 in dioxane (4µl, 2 equiv):

^{1}H NMR (400 MHz, Acetone) δ 6.16 – 6.08 (m, 4H), 5.96 – 5.87 (m, 1H), 5.36 (s, 5H).
^{31}P NMR (162 MHz, Acetone) δ -144.18.



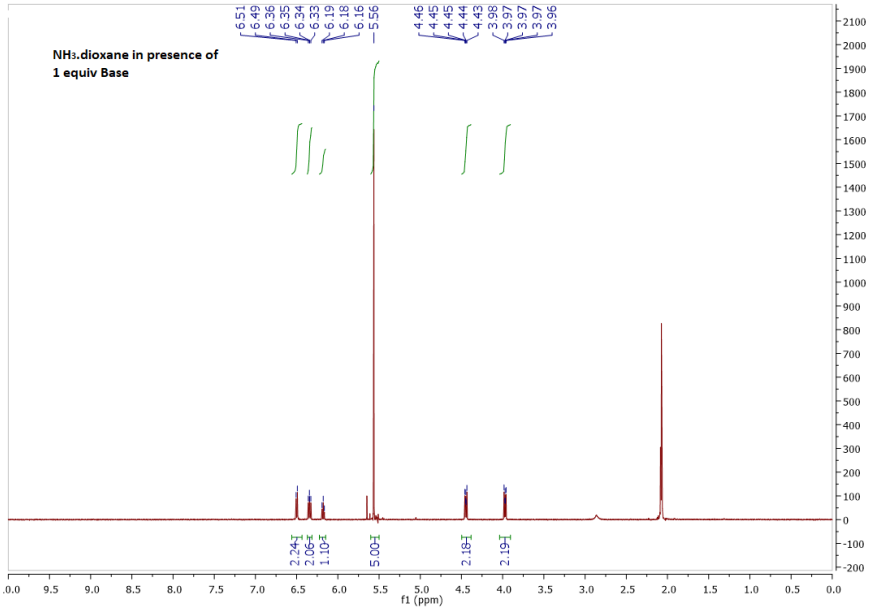
- NH_4OAC (16 mg, 2 equiv):

^{1}H NMR (400 MHz, Acetone) δ 6.11 – 5.89 (m, *J* = 30.7 Hz, 4H), 5.86 – 5.77 (m, 1H), 5.30 (s, 5H).
^{31}P NMR (162 MHz, Acetone) δ -144.57.



- NH_3 in dioxane (4µl, 2 equiv) in presence of Cs_2CO_3 (32 mg, 0.1 mmol):

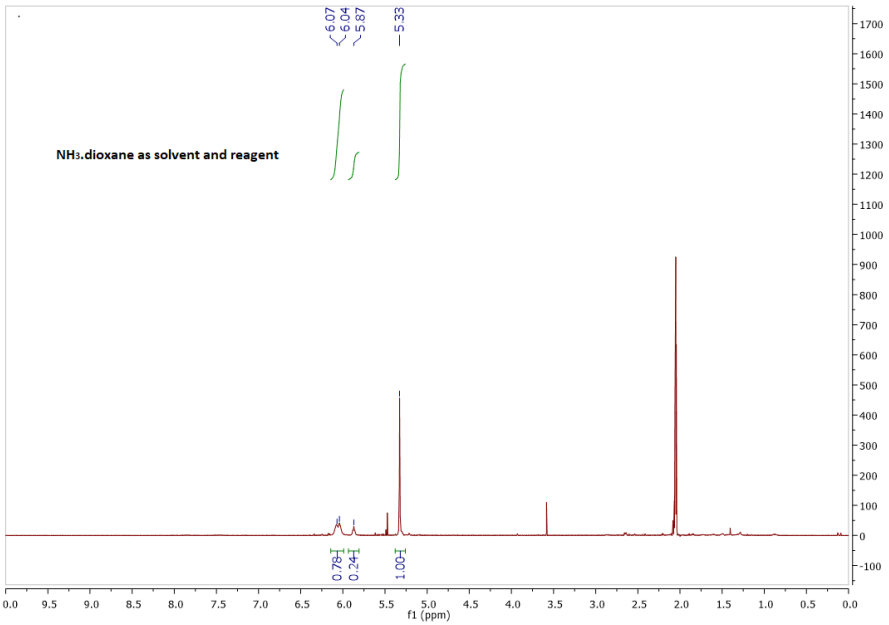
^{1}H NMR (400 MHz, Acetone) δ 6.50 – 6.44 (m, 2H), 6.32 (dd, *J* = 6.7, 5.6 Hz, 2H), 6.15 (t, *J* = 5.6 Hz, 1H), 5.53 (s, 5H), 4.46 – 4.40 (t, *J* = 5.2 Hz, 2H), 3.98 – 3.91 (t, *J* = 5.2 Hz, 2H). ^{31}P NMR (162 MHz, Acetone) δ -144.27.



Procedure for the reaction of phenol complexes in NH_3.dioxane

After standard cycles of evacuation and back-filling with argon, an oven-dried Schlenk flask equipped with a magnetic stirring bar was charged with the phenol complex **C_1** (40 mg, 0.1 mmol) . The tube was evacuated and back-filled with argon. And this procedure was repeated three times. Under a stream of argon, 2 ml of NH_3.dioxane were and added, followed by the addition of 0.1 ml of dry acetonitrile. The Schlenk is sealed under a positive pressure of argon, stirred under reflux for 12h. After allowing the reaction to cool to room temperature, the solvent was evaporated and the residue was dissolved in acetone and filtered through a short plug of celite and washed with acetone. The solution was evaporated to afford the new complex.

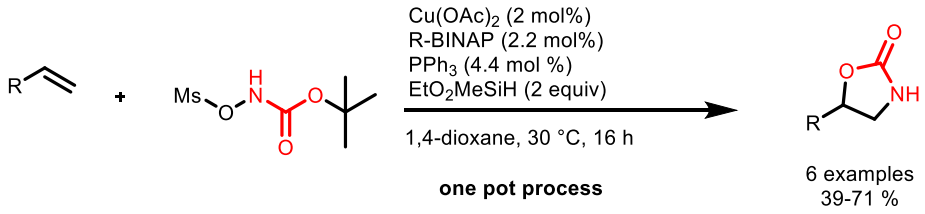
^{1}H NMR (400 MHz, Acetone) δ 6.14 – 6.00 (m, 4H), 5.87 (t, *J* = 4.5 Hz, 1H), 5.33 (s, 5H).
^{31}P NMR (162 MHz, Acetone) δ -144.23.



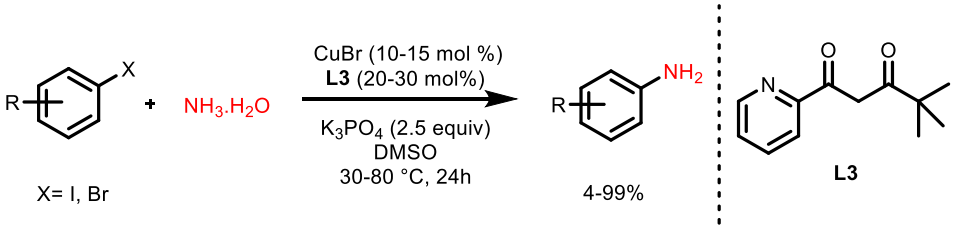
General conclusion

This thesis is a part of general research for novel, cheap and eco-friendly methods to valorize some subtrates and to synthesize molecules with hight interest and wide application in various fields such as material, pharmaceutical and organic chemistry. The main goal was the creation of new C-C and C-heteroatom bonds with high selectivity by using transition metal-catalysts.

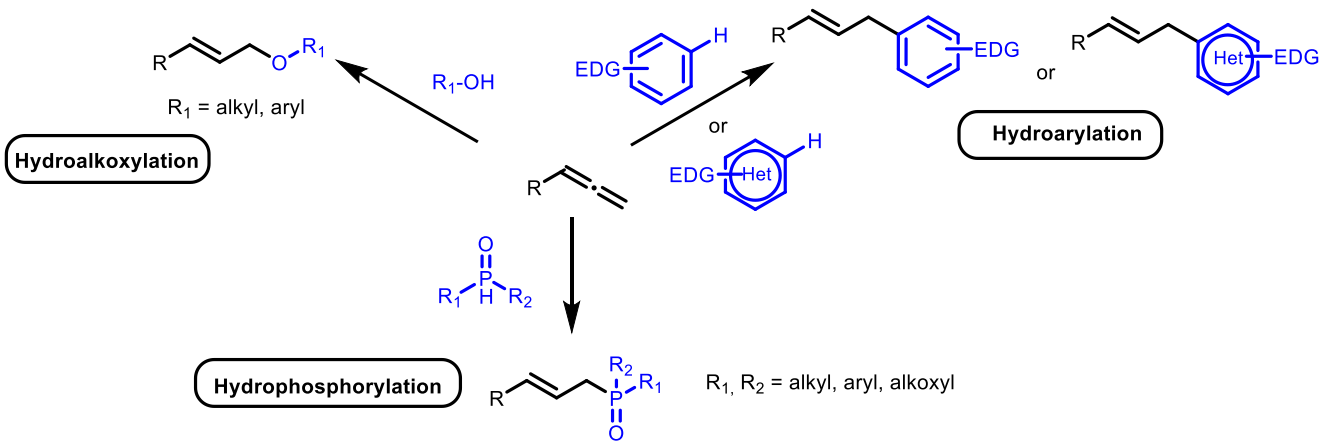
In the first part, we discovered a copper-catalytic system for alkenes difunctionalization with amino-oxygenated compounds. This method leads in one-pot process to the formation of oxazolidinone, which is an interesting moiety present in various bioactive molecules. Despite its interesting concept, this method showed a defect on the application field : the scope of alkenes was limited to a few molecules affording the corresponding oxazolidinone in low to moderate yields.



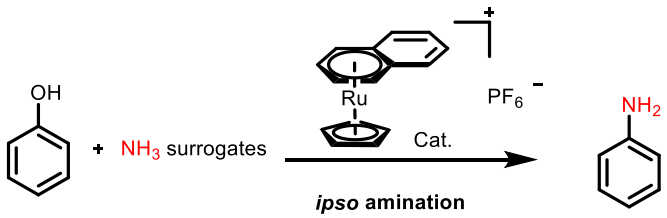
In the second part, novel pyridyl diketone ligands have been employed in ammonia arylation reaction. Associated to copper catalyst, this system led the amination of aryl iodides and bromides in mild temperature conditions to afford aniline derivatives which are valuable molecules for the material chemistry. This method tolerated a variety of substituents on the aromatic ring.



In the third part, we developed new systems for the allenes hydrofunctionalizations by using copper-catalysts. We elaborated the direct hydroarylation of allenes by using electron-rich aromatics and heteroaromatics to create a selective C-C_{Ar} bonds. Thus currently we are working on allenes hydroalkoxylation and hydrophosphorylation by using respectively alcohols and and organophosphorus compounds in order to create new C-O and C-P bonds. These methods do not require any additional ligand, and afford selectively the (*E*)-allylic products with total atom economy. These obtained products could be interesting key intermediates in organic chemistry.



In the last part, we investigated the developement of a novel ruthenium complex to allow the direct phenol amination which remains nowadays a big challenge. In order to decrease the phenol electron density and then to facilitate the nucleophilic attack on the carbon atom bearing the -OH, we proposed to complex the phenol ring to a ruthenium-cyclopentadienyl fragment. Thus we coud envisage the direct amination without any previous activation.



Résumé en français

Chapitre I : Synthèse d'oxazolidinone à partir d'alcènes par catalyse au cuivre

Les oxazolidinones sont des composés hétérocycliques à cinq chaînons. Ce sont des squelettes importants présents dans de nombreuses molécules de haute activité biologique. Leurs domaines d'utilisation sont très variés. Ils sont notament utilisés comme auxiliaires chiraux dans le domaine de la synthèse asymétrique depuis leur introduction par David Evans. De plus, cet hétérocycle est présent dans plusieurs médicaments comme le Tédizolide et le Linézolide.

Les oxazolidinones sont l'objet de recherches approfondies depuis plusieurs années, notamment afin de trouver de nouvelles voies d'accès simples et efficaces. Plusieurs méthodes ont été décrites pour synthétiser cet héterocycle à 5 chaînons à partir d'amino-alcools, d'aziridine, d'époxyde, d'alcène, d'alcool et d'amines propargylique.

Dans ce chapitre, nous souhaitons décrire la synthèse des oxazolidinones à partir des alcènes en utilisant un système catalytique au cuivre. Cette méthode produit ce composé cyclique en une seule étape.

Nous avons commencé notre étude en utilisant le styrène comme substrat modèle. Plusieurs amines secondaires et électrophiles ont été synthétisées au laboratoire et elles ont été testées pour cette réaction. L'amine **G** a donné les meilleurs rendements dans les tests préliminaires et donc a été utilisé ensuite pour l'optimisation des conditions.

Plusieurs paramètres ont été étudiés : le catalyseur et sa quantité, le ligand, le solvant, la température, la quantité de l'amine, la concentration et la durée de la réaction pour obtenir de meilleures conditions réactionnelles (Schéma 1).

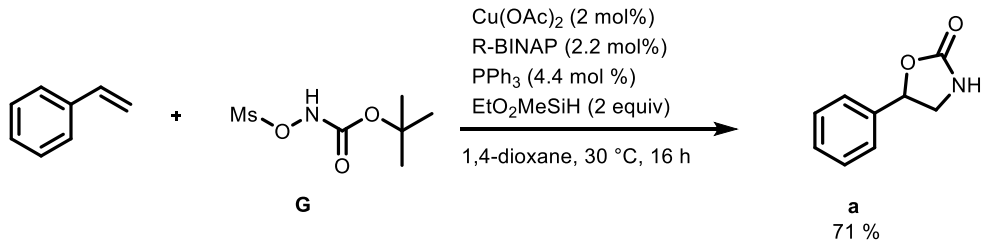


Schéma 1 : conditions optimisées de la synthèse d'oxazolidinone.

Par la suite, nous avons étudié la réactivité d'alcènes de natures différentes. La limitation de l'application de cette réaction sur nombreux alcènes est surprenante, surtout en ce qui concerne des alcènes similaires électroniquement mais qui ont réagi d'une manière complétement différente. Seulement 5 alcènes ont abouti à l'oxazolidinone après 16 heures de la réaction avec l'amine **G** sous les conditions présentées ci-dessus. Les produits désirés sont obtenus avec des rendements faibles à moyens (Figure 40).

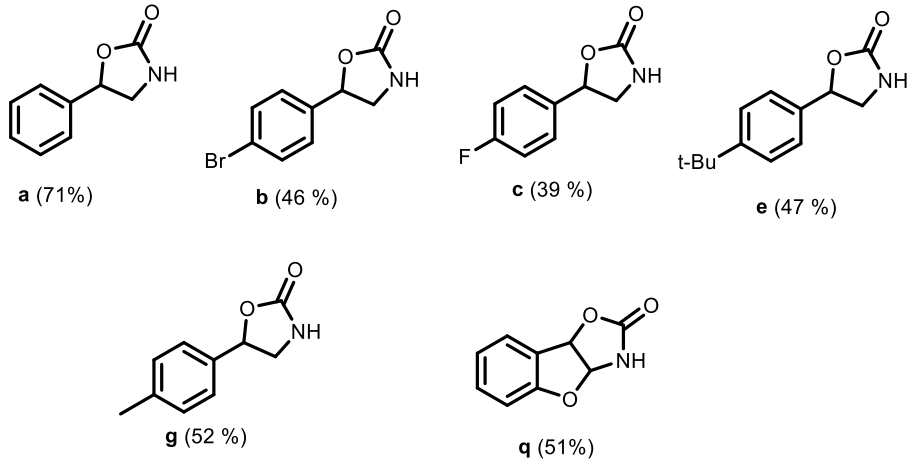


Figure 40 : les oxazolidinones formés et leurs rendements.

Il est important de noter que, malgé l'utilistion de plusieurs ligands chiraux, l'oxazolidinone obtenue est racémique. Des analyses en HPLC ont été réalisées et elles ont montré que le ligand ne contrôle pas la stéréochimie lors de l'étape de cyclisation, ce qui empêche le développement d'une méthode catalytique et énantiosélective. Cependant, nous avons utilisé le (*R*)-BINAP pour de raisons de coût (moins cher que le composé racémique) étant donné que le BINAP a donné la meilleure réactivité parmi les ligands testés.

Nous avons également tenté de comprendre le mécanisme de la formation de l'oxazolidinone. Nous supposons que cette réaction passe par la formation *in-situ* d'un intermédiaire important qui aboutit ensuite à la formation de l'oxazolidinone : En présence du système catalytique au cuivre l'amine réagit avec l'alcène pour former le *N*-Boc aziridine **A**. Il a été démontré que ce dernier peut subir en présence d'un acide de Lewis un réarrangement pour aboutir à l'oxazolidinone tout en libérant un équivalent d'isobutène (Schéma 2).

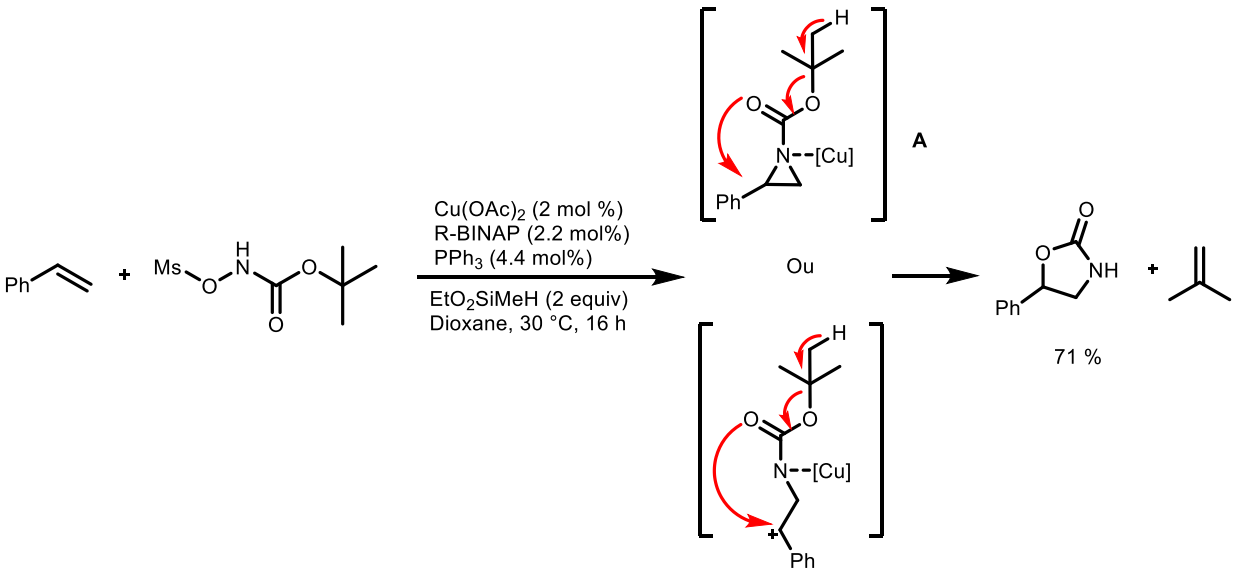


Schéma 2 : mécanisme proposé pour la synthèse d'oxazolidinone à partir d'alcène.

La di-fonctionnalisation des insaturations et particulièrement des alcènes est une transformation très importante pour la chimie organique et pharmaceutique. Dans ce projet, nous avons développé

une di-fonctionnalisation d'alcènes avec un composé amino-oxygéné. Cette réaction produit en un seule étape l'oxazolidinone d'une façon régioséléctive en partant d'un alcène.

Intéressés par cette réaction et par la valeur du cycle produit par cette méthode, nous visons à étendre cette méthode pour synthétiser d'autres hétérocycles qui ont également une haute valeur ajoutée et une activité intéressante comme l'oxothiazolidine et le dioxyde d'oxathiazolidine (Schéma 3).

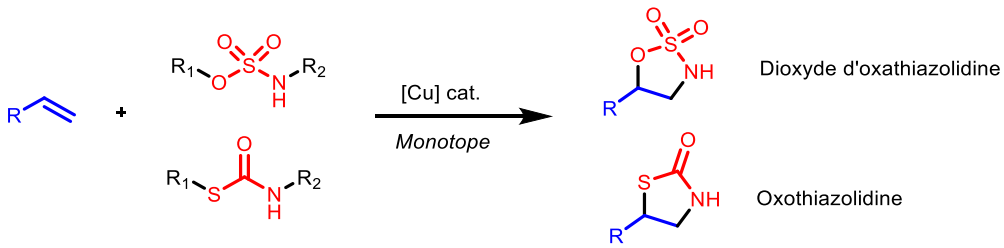


Schéma 3 : perspectives.

Chapitre II : Amination des aryles halogénés par catalyse au cuivre et en présence de ligands originaux

L'aniline est une molécule importante de l'industrie chimique pour la synthèse de produits pharmaceutiques, agrochimiques, et chimiques. Actuellement, 85% de la production mondiale de l'aniline est consommée pour la synthèse de 4,4'-diisocyanate de diphénylméthylène nommé MDI, qui est un monomère utilisé pour la synthèse industrielle de polyuréthane.

Pour répondre à ces demandes, plusieurs méthodes de synthèse de l'aniline et de ses dérivés ont été développées notamment à partir des aryles halogénés. Des nombreuses méthodes industrielles ont été découvertes en utilisant des conditions dures telles que des hautes pressions et des hautes températures ce qui limite la faisabilité d'amination sur certains aryles comme les hétéroaromatiques. En parallèle, plusieurs méthodes d'amination directes catalysées par des métaux de transition tels que palladium, nickel et cuivre ont été décrites (Schéma 4).

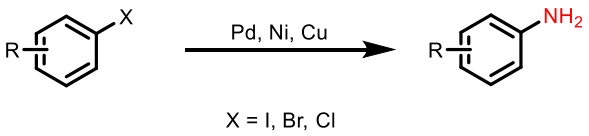


Schéma 4 : amination directe des aryles halogénés par catalyse aux métaux de transition.

Malgré le grand nombre de méthodes, la majorité souffrent d'inconvénients comme le cout du catalyseur, sa toxicité et son instabilité, et les conditions dures présentées par certaines méthodes. Pour ces raisons, il existe toujours un besoin pour le développement de systèmes simples et efficaces afin de réaliser l'amination des aryles halogénés dans des conditions douces.

Dans le cadre d'une collaboration avec l'équipe de Prof. Artur R. Stefankiewicz de l'université Adam Mickiewicz à Poznan, nous avons développé un nouveau système d'arylation de l'ammoniac en utilisant un catalyseur au cuivre. Une série de ligands de type pyridil dicétone (**L1**, **L2** et **L3**) ont été synthétisés par leur équipe (Figure 41), et engagés dans notre laboratoire dans les réactions d'amination des aryles halogénés.

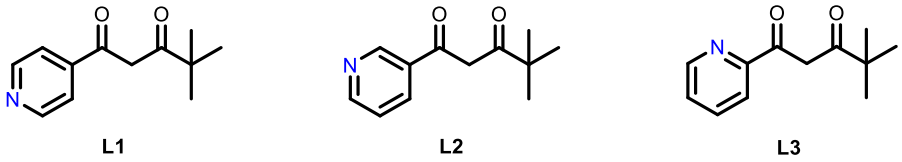


Figure 41 : ligands pyridil dicétones.

En utilisant ces ligands, nous avons réussi à réaliser l'amination d'aryles iodés à température ambiante (25-30 °C) en présence de 10 mol% de CuBr et d'une base dans le DMSO. Ces conditions sont compatibles avec nombreuses fonctions présentes sur le composé arylique (Schéma 5).

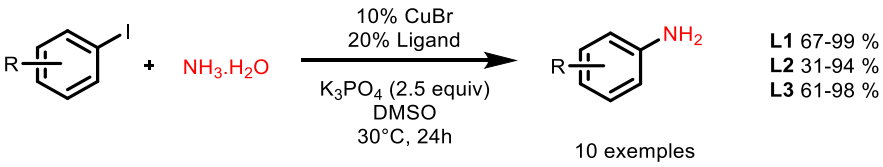


Schéma 5 : amination des aryles iodés.

Le ligand **L3** a donné les meilleurs rendements dans la majorité des cas avec les aryles iodés. Pour cette raison, il était choisi ensuite pour l'optimisation des conditions de l'amination des aryles bromés (Schéma 6).

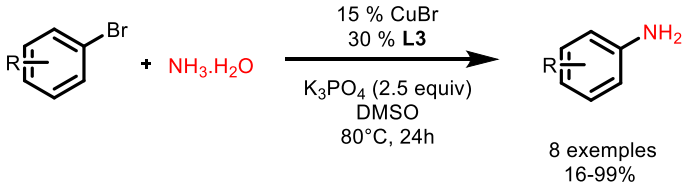


Schéma 6 : amination des aryles bromés.

Grâces à ces ligands facilement accessibles, simples et stables, l'amination des aryles iodés par l'ammoniac aqueux est réalisée dans des conditions douces, permettant l'application de cette méthode sur différents dérivés d'aniline avec une tolérance à de nombreux substituants. Nous avons également développé l'amination des aryles bromés, molécules plus abondantes et de bon marché.

En raison de leur efficacité et leur stabilité, ces ligands font toujours l'objet d'étude afin de les engager dans d'autres réactions de couplage catalysées au cuivre au sein de notre laboratoire.

Chapitre III : Hydrofonctionnalisations intermoléculaires d'allènes catalysées au cuivre

Depuis quelques années, notre laboratoire possède une expertise dans le domaine de la fonctionnalisation des allènes notamment pour l'hydrofonctionnalisation catalysée au cuivre; nous avons donc souhaité étendre et appliquer ce savoir-faire dans l'étude des nouvelles hydrofonctionnalisations pour créer des nouvelles liaisons C-C et C-Hétéroatome.

Récemment, notre équipe a élaboré un système catalytique au cuivre pour réaliser l'hydroamination des allènes, notamment les *N*-allenamides, les dérivés de sulfamides et les hétérocycles azotés. Par la suite, cette méthodologie a été étendue sur l'addition des carbones pro nucléophiles (comme les malonates, les dicétones et les céto-esters) et sur les acides carboxyliques. Ces méthodes ont abouti sélectivement à des produits allyliques sous la forme d'un seul stéréoisomère. Ces methodes de choix se caractèrisent par un contrôle total de la régio- et la stéréochimie, ainsi que d'une économie totale d'atomes.

En se basant sur ces travaux, nous avons commencé notre projet dans le but de créer des nouvelles liaisons C-C, C-O et C-P (Schéma 7).

Schéma 7 : équation générale de des hydrofonctionnalisations à réaliser dans ce chapitre.

- Hydroarylation intermoléculaire :

L'hydroarylation des allènes a été largement étudiée en utilisant des métaux tels que Pt, Au, Pd, Mn, Ru et plusieurs autres. Nous avons envisagé une hydroarylation directe catalysée au cuivre, en utilisant des (hétéro)-aromatiques électroniquement riches. Une fois que nous avons optimisé les conditions, nous avons appliqué cette méthodologie sur des aromatiques variés (Schéma 8). Il est important de signaler que nous avons obtenu sélectivement le produit linéaire.

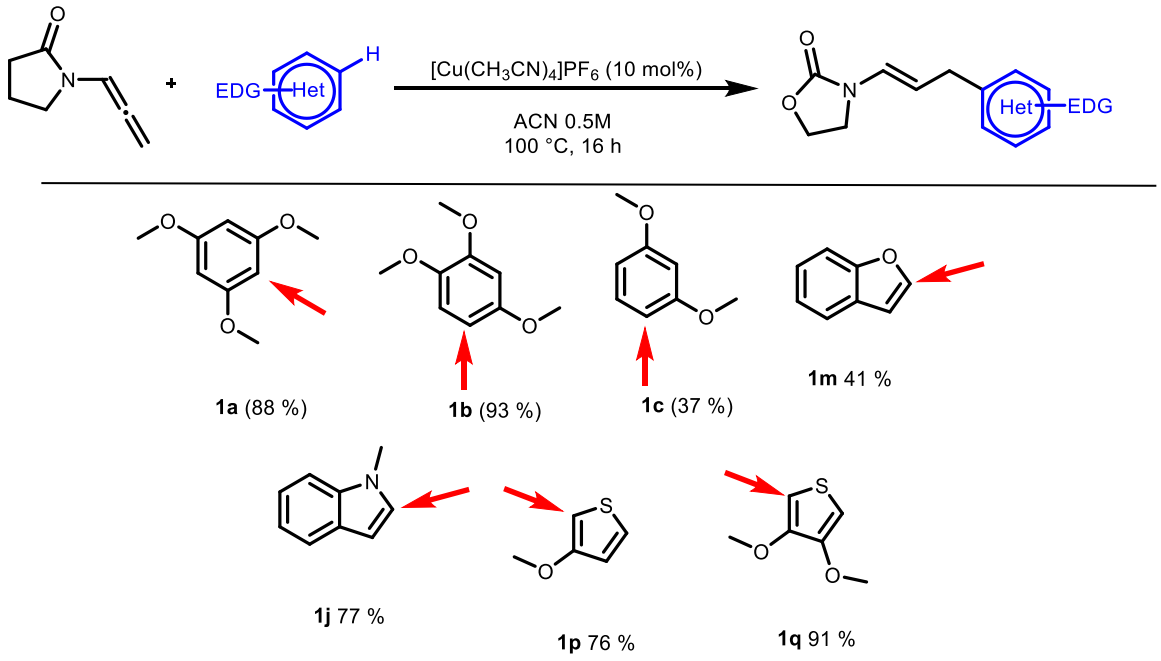


Schéma 8 : allylation des (hétéro)-aromatiques.

En parallèle, nous sommes actuellement en train d'étendre l'application de cette méthode sur différents allènes et particulièrement les allenamides et les dérivés de sulfamides (Figure 42).

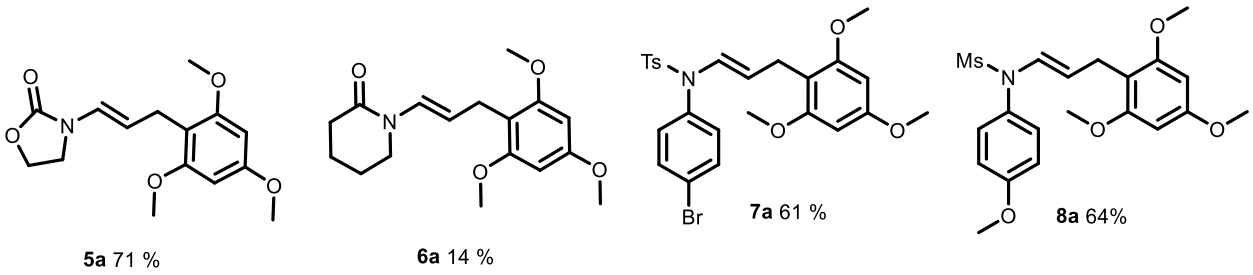


Figure 42 : hydroarylation des *N*-allenes.

- Hydroalkoxylation intermoléculaire :

Suite à ces travaux, nous avons souhaité synthétiser des éthers allyliques à partir des allènes par une réactions d'hydroalkoxylation. Nous avons donc commencé ce projet au laboratoire et nous avons réussi à additionner sélectivement les alcools sur le carbone terminal de l'allène. Pour le moment cette méthode est limitée aux alcools liquides, vu que ceux derniers sont utilisés comme solvants et réactifs en même temps (Schéma 9). Notre but sera d'appliquer cette méthode sur des alcools solides en trouvant les meilleures conditions.

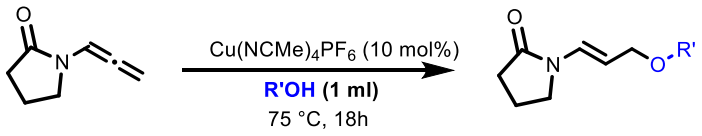


Schéma 9 : hydroalkoxylation de l'allenamide avec l'alcool comme solvant.

- Hydrophosphorylation intermoléculaire :

Dans le but de créer des nouvelles liaisons C-P, nous avons entrepris l'étude de la réaction d'hydrophosphorylation des allènes. Ce type de fonctionnalisation n'est pas très étudiée comme l'hydroarylation ou l'hydroalkoxylation, malgré le grand intérêt des produits qui peuvent être formés. Nos premières réactions avec l'oxyde de diphénylphosphine comme modèle ont donné des résultats très intéressants dans des conditions douces (Schéma 10).

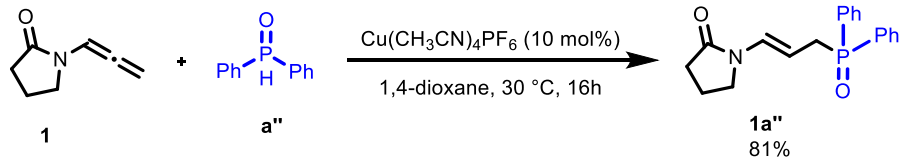


Schéma 10 : Hydrophosphorylation avec l'oxyde de diphénylphosphine

Encouragés par ces résultats, nous sommes en train d'étudier les conditions afin d'appliquer cette méthodologie sur des phosphonates.

Chapter IV : Amination directe des phénols *via* des complexes de ruthénium

Le phénol est l'une de matières premières la plus abondante de goudron de houille et constitue l'unité de base de la lignine. Pour ces raisons, le phénol peut servir comme alternative intéressante des aromatiques, en particulier les aryles halogénés pour synthétiser des molécules de hautes valeurs et intérêts.

Le phénol possède une fonction hydroxyle acide et une liaison C-O à haute énergie de dissociation. Ces caractéristiques forment un obstacle qui empêchent la fonctionnalisation directe du phénol en position *ipso*. En raison de ces difficultés, il est nécessaire toutefois de transformer le phénol en un de ses dérivés afin de faciliter sa fonctionnalisation. Par exemple, l'amination du phénol a été réalisée à partir d'éthers, d'esters, de sulfonates et de carbonate en utilisant des systèmes catalytiques au palladium et au nickel (Schéma 11).

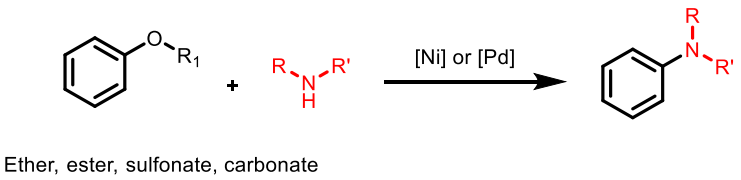


Schéma 11 : amination de dérivés de phénol catalysée au nickel et au palladium.

Dans ce chapitre, nous nous sommes intéressés à un nouveau système catalytique pour réaliser l'amination directe du phénol et de ses dérivés sans aucune transformation ou activation préalable de la fonction -OH. Notre point de départ est l'affaiblissement de la liaison C_{Ar}-O en augmentant l'éléctrophilicité de ce carbone ce qui facilite ensuite la substitution directe sur cet atome. En général, la complexation d'un métal à un aromatique peut répondre à cet objectif en diminuant la densité électronique du corps aromatique, augmentant par la suite l'électrophilie. Pour illustrer notre idée, nous avons choisi les complexes de ruthenium qui sont géneralement des complexes stables, et notamment [CpRu($C_{10}H_8$)]X où le naphthalene grâce à son caractère labile peut s'échanger facilement avec d'autres aromatiques comme le phénol dans notre cas (Schéma 12).

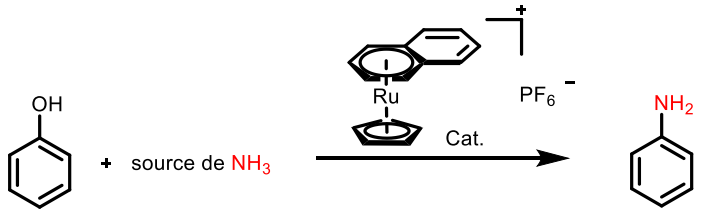


Schéma 12 : amination directe du phénol *via* des complexes au Ru.

Dans un premier temps nous avons trouvé les bonnes conditions pour accéder à une série de dérivés de phénol complexés au ruthénium et possédant des effets électroniques différents (Schéma 13).

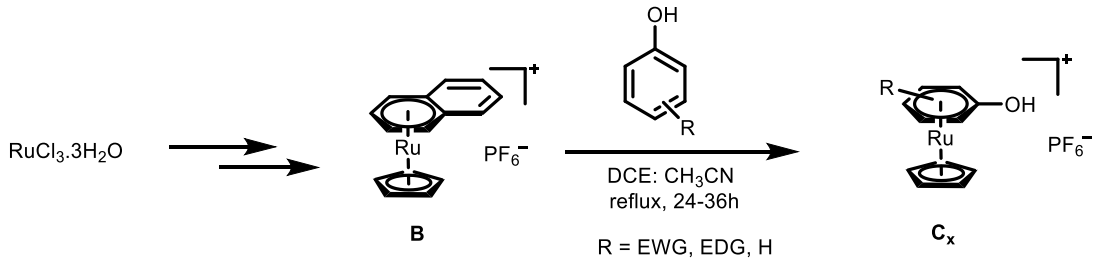


Schéma 13 : synthèse des complexes PhOH-Ru par échange du naphtalène par le phénol.

Par la suite, plusieurs sources d'amine ont été testées afin de réaliser la substitution directe sur le carbone portant la fonction –OH. Cette étape est actuellement en cours d'étude (Schéma 14).

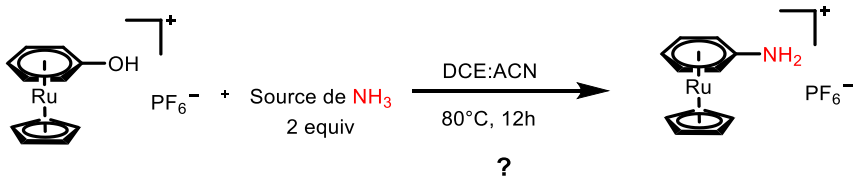


Schéma 14 : l'étape d'amination.

Après avoir réalisé cette réaction en stœchiométrique, la prochaine étape sera de faire cette réaction en catalytique et d'appliquer ensuite cette méthode sur une série des phénols biosourcés afin de valoriser ces derniers.

Résumé

Cette thèse se situe dans le cadre général de la recherche de nouvelles méthodes de synthèse peu couteuses et éco-compatibles permettant de valoriser certaines molécules en accédant à des composés intéressants dans plusieurs domaines comme la chimie des matériaux, pharmaceutique et organique. L'objectif consiste à créer des nouvelles liaisons C-C et C-hétéroatome sous un contrôle de sélectivité par catalyse avec des métaux de transition.

Dans une première partie, une difonctionnalisation des alcènes a été réalisée par catalyse au cuivre pour aboutir à l'oxazolidinone qui comporte un squelette important présent dans de nombreuses molécules de haute activité biologique.

Dans la deuxième partie, des ligands pyridil dicétones associés à un catalyseur de cuivre ont été employé dans l'arylation de l'ammoniac aqueux. Ce système s'applique au couplage à partir des aryles iodés et bromés dans des conditions douces pour donner l'aniline, un intéressant précurseur de molécules d'intérêt surtout pour la chimie de matériaux.

Dans la troisième partie, des réactions d'hydrofonctionnalisation des allènes catalysées au cuivre ont été développées pour créer de nouvelles liaisons C-C, C-O et C-P. Ces réactions permettent d'accéder sélectivement à des produits allyliques qui pourront être des intermédiaires intéressants dans la chimie organique.

La dernière partie consiste à mettre en œuvre un nouveau complexe de ruthénium visant à réaliser une amination directe du phénol sans aucune pré-activation.

Mots-clés : alcènes, aniline, cuivre, allènes, hydrofonctionnalisation, phénol, ruthénium.

Abstract

This thesis is a part of general research for novel, cheap and eco-friendly methods for the valorization of some subtrates and for the synthesis of interesting molecules in various fields such as material, pharmaceutical and organic chemistry. The main goal is to create new C-C and C-heteroatom bonds with high selectivity by using transition metal-catalysts.

In the first part, a copper-catalyzed alkenes difunctionalization has been realized to afford oxazolidinone, which contains an interesting moiety present in various bioactive molecules.

In the second part, novel pyridyl diketone ligands associated to a copper catalyst have been employed in ammonia arylation reaction. This system led the amination of aryl iodides and bromides in mild temperature conditions to afford aniline derivatives, valuable molecules for the material chemistry.

In the third part, we developed copper-catalyzed hydrofunctionalizations of allenes to create new C-C, C-O and C-P bonds. These methods afford selectively the allylic products, that could be valuable key intermediates in organic chemistry.

The last part consists in the developement of a novel ruthenium complex to allow the direct phenol amination without any previous activation.

Key-words : alkenes, aniline, copper, allenes, hydrofunctionalization, phenol, ruthenium.