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Approaches towards C-H carboxylation mediated by group 11 metal centres.

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Abbreviations

TMP 2,4,6 Trimethylphenol

TMs Transition metals

ILs Ionic liquids

PMHS polymethylhydrosiloxane

DCM Dichloromethane

ACN Acetonitrile

Abstract

Carbon Dioxide is the most abundant and accessible source of carbon on Earth. It is non-toxic, low cost and renewable. Furthermore, the increasing concentration of CO_2 is the main cause of Greenhouse Effect. Thus, the availability of several processes which use It for building C-C bonds seem very attractive.

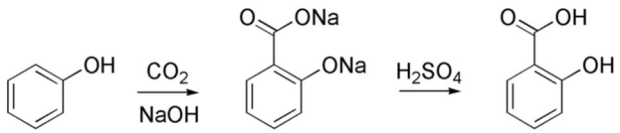
Several catalytic couplings of CO_2 with energy-rich substrates and aromatic substrates for the construction of C-O and C-N bonds have been already widely explored. However, owing to the thermodynamic stability and high oxidation state of CO_2, its coupling with aromatic substrates is traditionally achieved using highly reactive organolithium or Grignard reagents. All these methods suffer drawbacks of low functional group compatibility, and they all need a pre-functionalization step to be applied in organic synthesis. To avoid these issues many methodologies have been developed over the last two decades for the carboxylation of different organometallic reagents. Nowadays, C-H activation is one of the most encompassing transformations in Organometallic Chemistry since It allows efficient functionalisation of alkynes, heterocycles and aromatic substrates and it is starting to be applied to carboxylations as well.

This work focuses on carboxylations through C-H activation mechanisms considering the most promising transition metals recently studied for these processes which are: Copper, Silver and Gold. The group 11 metals are the most promising since their strong electrophilic character, their ability to easily metallate acidic C-H bonds and their relatively simple chemistry which reduces the possibility of parasite processes make it possible to combine their catalytic action with others catalytic cycles.

INTRODUCTION

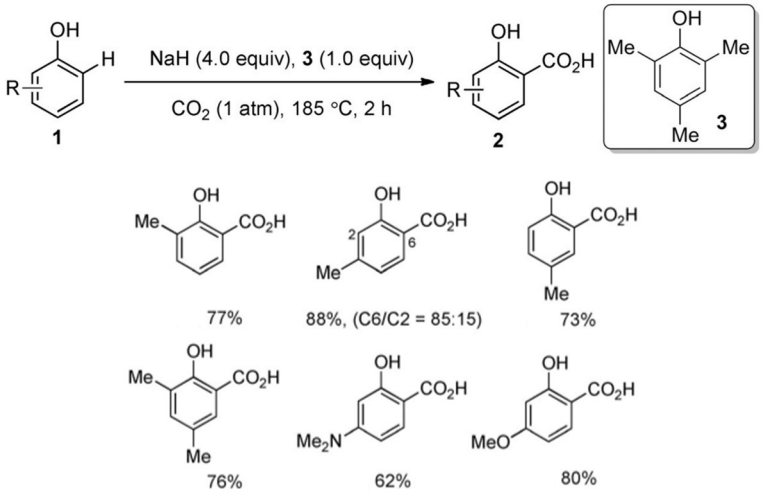
1.1 Base Mediated carboxylations

The first example of C-H carboxylation was developed by Kolbe and Schmitt in the 1860's and It is still widely used in industry today.[1] It is one of the most important and well-known carboxylation reaction providing direct access to salicylic acid through the ortho carboxylation of phenoxides with CO_2.



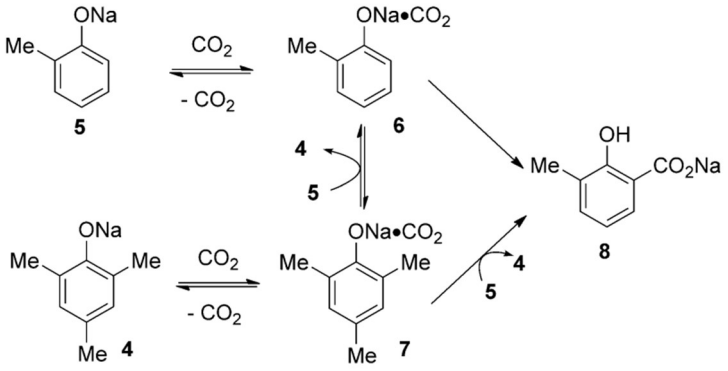
Scheme 1. *Kolbe and Schmitt C-H carboxylation.*

This process is achieved in good yields using high CO_2 pressure and temperature. Additionally, the isolation of the dry phenoxide intermediate is necessary since water can inhibits the Kolbe-Schmitt carboxylation [2]. That is because the carboxylation process happens through weak coordination between the alkali metal ions and CO_2 and water can strongly coordinate with the alkali metal phenoxide inhibiting the carboxylation or hydrolysing the metal phenoxide affording the initial phenol.



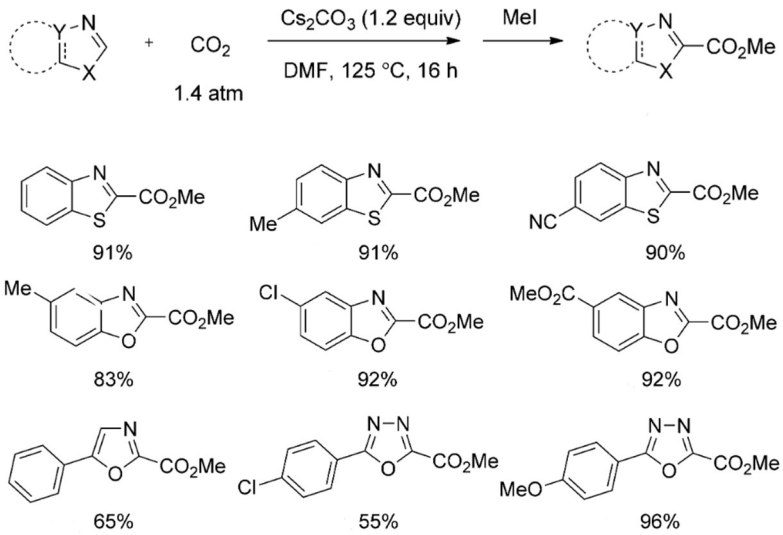
Scheme 2. *Selected examples of phenol carboxylation.*

In 2016, the Larrosa group developed the first protocol for a Kolbe–Schmitt carboxylations that occurs efficiently under 1 atm of CO_2[3]. Their protocol employs NaH as base instead of Na_2CO_3 to avoid the water formation, making the process workable as a one-pot reaction. In addition, they discovered that adding 2,4,6-trimethylphenol (TMP) as a recyclable additive the carboxylation rate is significantly increased even at reduced CO_2 pressures. The electrophilic aromatic substitution at phenoxide is the most accepted mechanism for this reaction. It is proposed that sodium 2,4,6-trimethylphenoxide **4**, generated in situ from **3** and excess NaH, may play a role in aiding CO_2 fixation, although **4** is inert toward ortho-carboxylation itself.

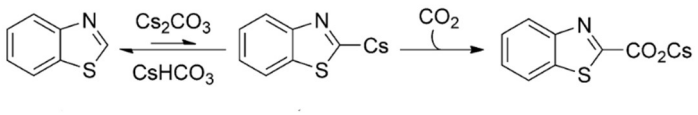


Scheme 3. *Proposed mechanism for 2,4,6-trimethylphenol (TMP)-promoted carboxylation.*

Recently, beside the C-H carboxylation of phenols, much attention has been given to base mediated C-H carboxylation of heteroarenes. In 2010, Hu and co-workers developed a methodology for the C-H carboxylation of benzothioazole substrates under 1.4 atm CO_2[4]. They discovered that the process proceeds well when using LiOtBu and Cs_2CO_3 as bases, whereas K_2CO_3, NaOMe, NaOH, and KOH were found to be ineffective. Further investigations revealed that some of the heteroaromatic carboxylic acids are unstable in solution and slowly revert to the heteroarene upon loss of CO_2. Considering this, the carboxylated compounds were instead isolated as the corresponding methyl esters. The esterification is usually carried out by reaction with an alkyl halide or trimethylsilyldiazomethane ($TMSCHN_2$). Moreover, benzoxazole, oxazole, and 1,3,4-oxadiazole derivatives were also found to be compatible with this process, leading to the corresponding carboxylic acid derivatives in good yields. The proposed mechanism proceeds with Cs_2CO_3 mediated deprotonation of the C-H bond at the C2 position of benzothiazole followed by fixation of CO_2. (*scheme 4*)

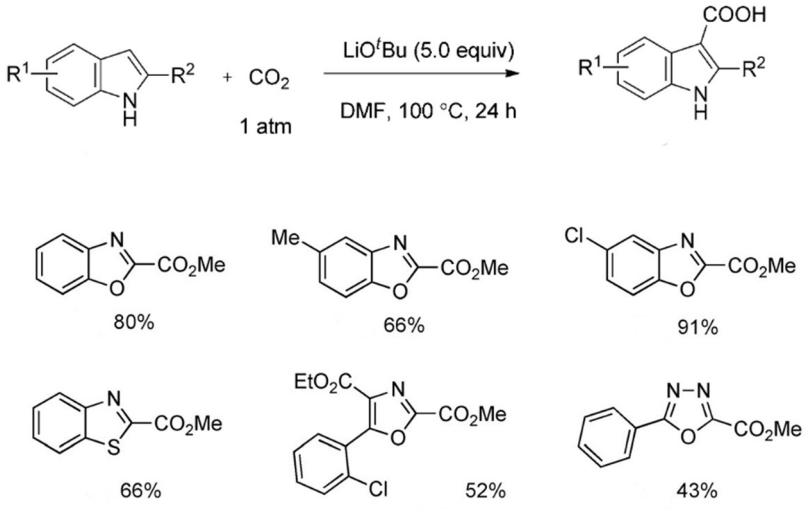


Scheme 4. *Selected examples of Cs_2CO_3 mediated carboxylation.*



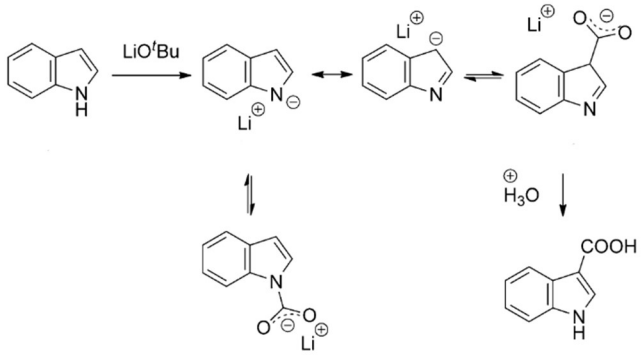
Scheme 5. *Proposed mechanism for Cs_2CO_3-mediated carboxylation.*

Fenner and Ackermann found that KOtBu enabled the efficient C-H carboxylation of heteroarenes with a wide substrate scope such as benzoxazole, benzothiazole, oxazole, and 1,3,4-oxadiazole derivatives [5] . If compared to the Cs_2CO_3 mediated process, the use of KOtBu allows for carboxylation at a relatively lower reaction temperature and at only 1atm CO_2 pressure. The authors suggest a mechanism analogous to the process with Cs_2CO_3. In 2012, the Kobayashi group found that LiOtBu allowed the formation of indole-3-carboxylic acids under ambient CO_2 pressure, proving that LiOtBu mediates carboxylation of indoles as well [6]. The process is compatible with both electron-rich and electron-poor substituents and is applicable to pyrrole derivates as well.



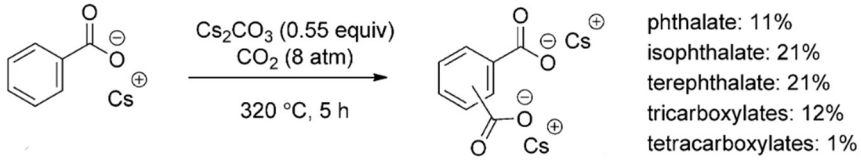
Scheme 6. *Selected examples of KOtBu-mediated carboxylation.*

The authors proposed a mechanism that starts with the deprotonation at the most acidic N-H proton. This anion can be initially reversibly captured with CO_2 to form N-centered carboxylate, but this compound eventually reacts at the high temperatures of the reaction to form the C3-carboxylated product. It must be observed that the free N-H is essential for this carboxylation, as the more nucleophilic N-methyl indole did not undergo base-mediated carboxylation under the reported conditions. This fact suggested that the reaction may proceed through electrophilic aromatic substitution rather than deprotonation of the C-H bond at the C3 position of indoles.



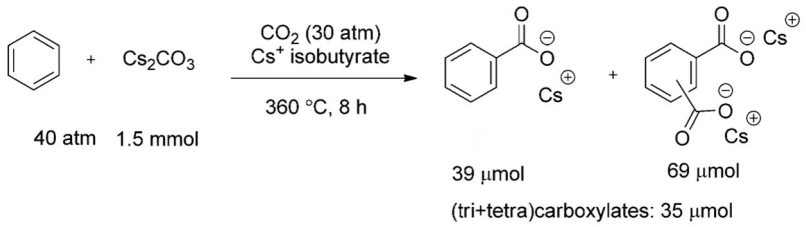
Scheme 7. *Proposed mechanism for carboxylation of indole.*

Recently, Kanan et al. proved that Cs_2CO_3 or K_2CO_3 molten salts can deprotonate poorly acidic C-H bonds (pKa > 40), to afford carbon nucleophiles that can then react with CO_2 to form carboxylates[7]. They were able to obtain furan-2,5-dicarboxylic acid from the carbonate promoted carboxylation of 2-furoic acid. The process was tested under a flow of CO_2 obtaining good yields and under 8 atm of CO_2 observing the maximum efficiency. Starting from these encouraging results, Kanan and co-workers tried to perform a similar process on a benzoate, a much weaker acid, obtaining a successful result. They were able to obtain a mixture of phthalates and tri- and tetra-carboxylates from the heating of the cesium benzoate in the presence of 0.55 equivalents of Cs_2CO_3 at 320°C and 8 atm of CO_2.



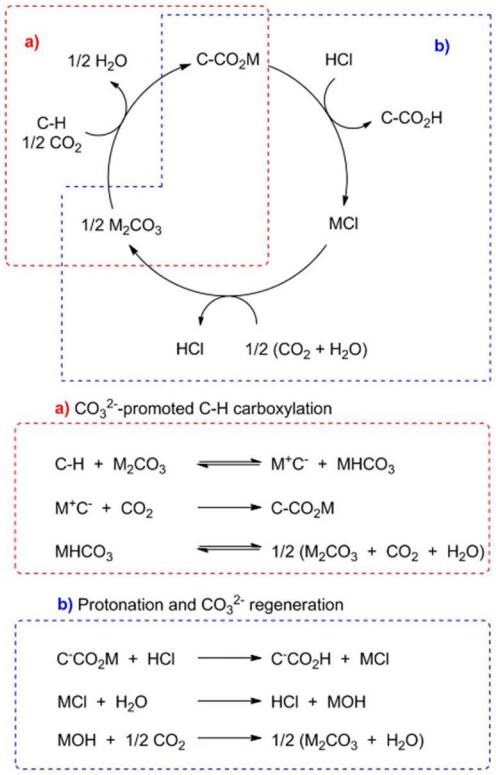
Scheme 8. *Carbonate-promoted carboxylation of benzoate.*

Benzene can be carboxylated through a base catalysed C-H carboxylation as well, but in more extreme conditions due to the larger entropic penalty and the possible lower solubility of benzene in the molten salt. Kanan and co-workers managed to obtain It in the presence of cesium isobutyrate additive, at 380°C under 30 atm CO_2 pressure and 40 atm benzene pressure. It is important to note that the cesium isobutyrate molten component is critical for the success of the reaction, since Cs_2CO_3 does not melt at 380 °C in the absence of cesium isobutyrate.



Scheme 9. *Carbonate-promoted carboxylation of benzene.*

The same authors envisioned that a M_2CO_3 reversibly deprotonates a C-H bond to generate $MHCO_3$ and a carbon-centered nucleophile M^+ C^- that could attack CO_2 to form C-CO_2M. The decomposition of $MHCO_3$ results in a net consumption of 0.5 eq of M_2CO_3 and CO_2 per C-CO_2M produced. The C-CO_2M could be protonated by treatment with HCl to form the carboxylic acid and by-product MCl. The metal salt MCl could then be processed by electrodialysis to regenerate M_2CO_3 and the acid HCl [8]. In this regard, this whole cycle would effectively transform C-H into C-CO_2H using only CO_2 and no other stoichiometric reagents.



Scheme 10. *Possible pathways for carbonate-promoted carboxylation of aromatics.*

1.2 Lewis-acid-mediated carboxylation

Friedel and Crafts proved that a minor amount of benzoic acid was obtained when CO_2 was bubbled trough a mixture of benzene and aluminium chloride [9]. They suggested this process may involve an initial complex between benzene and Al_2Cl_6. with subsequent formation of phenyl aluminium dichloride intermediates ($PhAl_2Cl_5$). (*scheme 11*).However, due to the low electrophilicity of CO_2 and the side-reactions attributed to the strong Lewis-acidity of aluminium-based compounds, the carboxylic acids are generally obtained in poor yields when using this procedure [10].

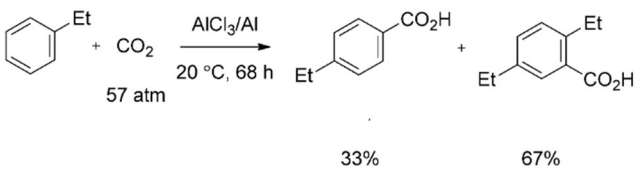
$$C_6H_6 + Al_2Cl_6 \longrightarrow C_6H_5Al_2Cl_5 + HCl$$

$$C_6H_5Al_2Cl_5 + CO_2 \longrightarrow C_6H_5COOAl_2Cl_5$$

$$C_6H_5COOAl_2Cl_5 + H_2O \longrightarrow C_6H_5COOH + Al_2Cl_5OH$$

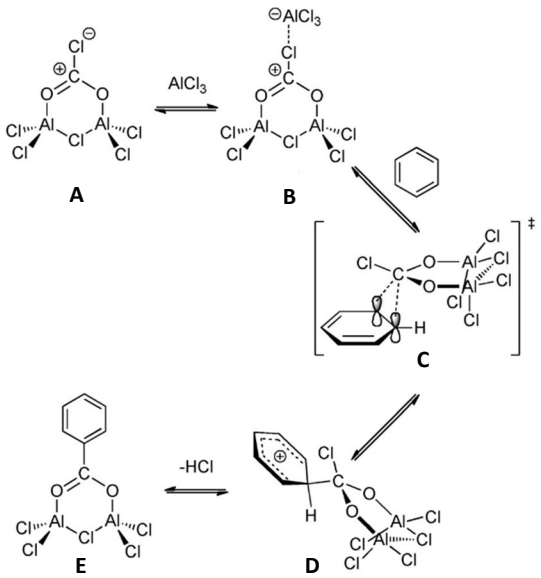
Scheme 11. *Possible pathways for the carboxylation of benzene promoted by Lewis-acids.*

Recently, Olah and Prakash reported that the addition of aluminium metal powder improves the arene carboxylation yields [11]. It presumably scavenges the HCl liberated in the process, shifting the equilibria toward product formation. Moreover, the $AlCl_3$ generated in situ upon reaction of Al with HCl further promotes carboxylation. This direct carboxylation could be carried out at moderate temperatures in good-to-excellent yield on a wide variety of arenes. The more active substrates such as mesitylene underwent the carboxylation to the corresponding acid with 80 % yield even at 20 °C. Conversely, deactivated aromatics such as benzene halides gave relatively low yields and nitrobenzene substrates were not carboxylated. Unfortunately, among alkylbenzenes only methylbenzenes are suited toward selective carboxylation as other homologues tend to disproportionate when treated with anhydrous $AlCl_3$/Al, decreasing the yield of the desired carboxylic acids (*scheme 12*).



Scheme 12. *AlCl3/Al-promoted carboxylation of alkylbenzenes.*

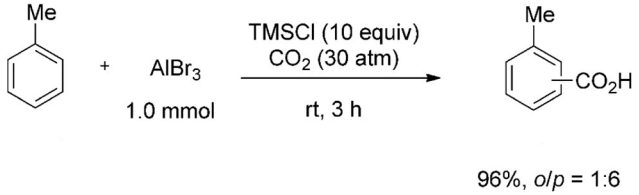
To investigate the reaction mechanism, density functional theory (DFT) studies on the activation process were carried out. The calculations favour a pathway involving the formation of a CO_2–$AlCl_3$ complex over the previously proposed formation of $PhAlCl_2$. Based on these calculations a new mechanistic pathway was proposed (*scheme 13*) Initial activation of CO_2 by two molecules of aluminium chloride affords six-membered ring CO_2–$(AlCl_3)_2$ complex **A**. In the presence of a further $AlCl_3$ molecule, **A** would react with benzene via transition state **C** to give intermediate **D**. Finally, re-aromatization with loss of HCl affords aluminium carboxylate **E**.



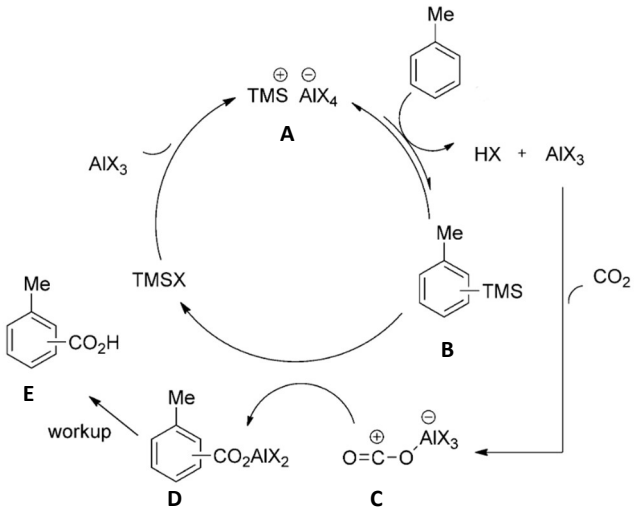
Scheme 13. *Possible pathways for $AlCl_3$/Al-promoted carboxylation of alkyl-benzenes.*

More recently, Munshi and co-workers found that the carboxylation of toluene proceeded more efficiently by holding $AlCl_3$ under pressured CO_2 (ca. 70 atm) for 1 h prior to the addition of toluene. This manipulation enables the carboxylation to occur with weaker Lewis's acids, such as $SnCl_4$, $MoCl_5$, or $TiCl_4$ without appreciable loss of product yield.[12] These observations further support Olah's mechanism of Lewis acid activation of CO_2.

Hattori and co-workers found that the carboxylation of aromatic compounds with CO_2 can be significantly promoted by the addition of a large excess of chlorotrimethylsilane (TMSCl). Noteworthy, the reaction proceeds under room temperature at 30 atm of CO_2 pressure [10] .The authors suggested that TMSX (X = Cl or Br) could be activated in the presence of the AlX_3 to form $TMSAlX_4$ **A** (*scheme 14*). These species would then silylate the aromatic substrate through an electrophilic aromatic substitution, affording arylsilane **B** and recovering AlX_3. Subsequently, CO_2-AlX_3 complex **C** can react with the arylsilane **B** to give aluminium carboxylate **E**, simultaneously regenerating TMSX at the expense of an equimolar amount of AlX_3. This step would be favoured by the stabilizing effect of the Si-C bond on the developing positive charge. The authors propose that the silylation step is an equilibrium process, thus justifying the requirement of a large excess of TMSX reagent to ensure that the reaction proceeds in high yields. However, this explanation for the need of a large excess of TMSX seems unlikely if, as proposed, the step forming A is irreversible as the quantity of **A** would be determined by the concentration of limiting reagent AlX_3.

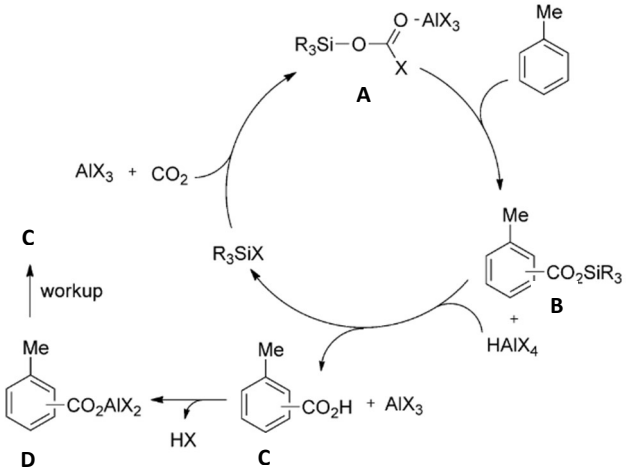


Scheme 14. *Lewis-acid-mediated carboxylation in the presence of TMSCl.*



Scheme 15. *Proposed mechanism for trimethylsilyl chloride (TMSCl)-promoted carboxylation.*

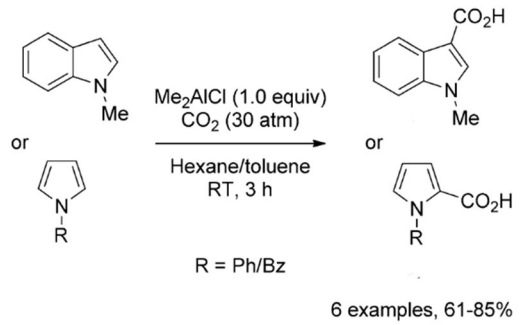
Subsequently, Hattori's group further extended this work showing that a variety of trialkyl or triaryl-silyl chlorides efficiently promote the $AlBr_3$-mediated carboxylation of aromatic compounds [10] .Triphenyl silyl chloride performed best among the silyl chlorides tested and, especially when polycyclic arenes were used, almost quantitative yields were obtained with high regioselectivity. Since Ph_3SiCl is recovered at the end of the reaction, the authors suggested that the silyl halides may act as catalysts in the carboxylation, although they are required in excess. In a revision to their previous proposal, the authors suggested that silyl chlorides promote carboxylation by reacting with CO_2 in cooperation with AlX_3 to give haloformate **A** like active species (*scheme 16*) which could react with the arene to give a silyl ester **B** and the superacid $HAlX_4$. The decomposition of in the presence of $HAlX_4$ leads to the carboxylic acid and regenerates the trialkylsilyl chloride R_3SiX. Finally, the carboxylic acid reacts with AlX_3 to afford an aluminium carboxylate 40 at the expense of an equimolar amount of AlX_3.



Scheme 16. *Revised mechanism for R_3SiX-promoted carboxylation.*

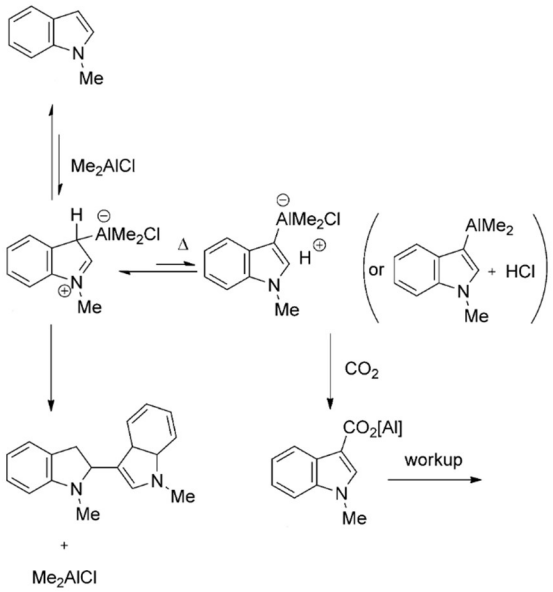
1-Substituted indoles and pyrroles can also be efficiently carboxylated under CO_2 pressure (ca. 30 atm) by using dialkylaluminum halides (Me_2AlCl) instead of aluminium trihalides [13]. This method is applicable to the regioselective carboxylation of 1-methylindoles, 1-benzylpyrroles, and 1-phenylpyrroles to afford the

corresponding indole-3-carboxylic acids and pyrrole-2-carboxylic acids in good yields. Unprotected simple indole or pyrrole could also undergo carboxylation, but low yields resulted.



Scheme 17. *Lewis-acid-mediated carboxylation of indoles and pyrroles.*

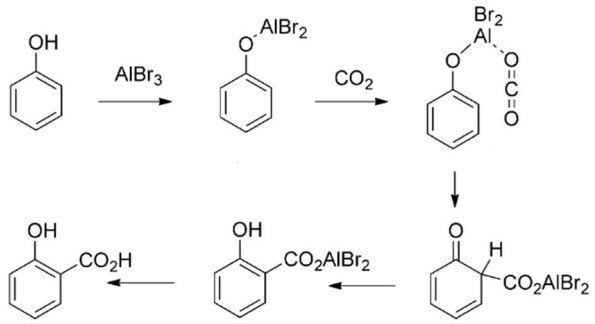
Hattori et al. suggested that a zwitterionic specie is formed initially through electrophilic addition of Me_2AlCl to 1-methylindole, followed by deprotonation to the aluminium complex and carboxylation (Scheme 17) [14]. The initial equilibrium is proposed to lie significantly toward the starting materials and it can be displaced by the carboxylation under high pressure of CO_2. Notably, HCl may be eliminated from zwitterionic specie to form indolylaluminum instead of the aluminium complex.



Scheme 18. *Lewis-acid-mediated carboxylation of indoles and pyrroles.*

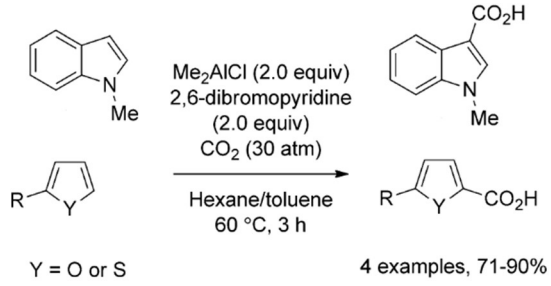
The same treatment of thiophenes and benzothiophenes with $EtAlCl_2$ under pressurized CO_2 gave the corresponding carboxylic acids in up to 90 % yield [15]. Also, fused-ring aromatic compounds, such as naphthalene, anthracene, and phenanthrene, could undergo Lewis-acid-mediated carboxylation under CO_2 pressure (ca. 30 atm), giving 1-naphthoic acid, 9-anthracenecarboxylic acid, and 9-phenanthrenecarboxylic acid, respectively [16].However, placing an electro withdrawing group on the fused-ring aromatic compounds completely hindered carboxylation. A plausible mechanism may involve the attack of a Lewis-acid-activated CO_2 molecule on the aromatic ring to form an arenium ion, followed by re-aromatization to give a carboxylic acid after aqueous workup. Salicylic acid derivatives have long been synthesized using the Kolbe–Schmitt reaction mediated by a base. However, Iijima and Yamaguchi found that the carboxylation of phenol with

CO_2 (ca. 80 atm) could also take place in the presence of a Lewis acid at moderate temperatures [11]. Among the Lewis acids investigated, $AlBr_3$ was found to be the most efficient, leading to the salicylic acids in approximately 70% yields. The proposed reaction mechanism involved the formation of phenoxyaluminum dibromide from phenol in the presence of $AlBr_3$. The intermediate could react with CO_2 to produce the CO_2 complex, which after ortho-carboxylation and re-aromatization afforded the aluminium salt of salicylate. Simple workup of the salicylate furnished the salicylic acid. This proposed mechanism is like the Kolbe Schmitt reaction, proceeding via an electrophilic aromatic substitution.



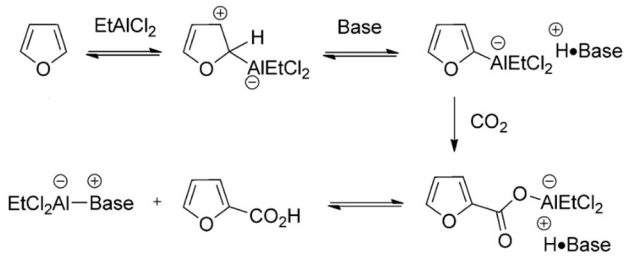
Scheme 19. *Proposed mechanism for the carboxylation of phenol mediated by a Lewis acid.*

It may be expected that bases would be incompatible with Lewis-acid-mediated carboxylations. However, Tanaka, Hattori, and co-workers developed a method for C-H carboxylation with CO_2 mediated by a combination of $EtAlCl_2$ and 2,6-dibromopyridine as a weak base [14].This method allows indole, thiophene, and furan derivatives to be carboxylated to the corresponding carboxylic acids. It is important to note that the protocol also enables a variety of alpha arylalkynes and trialkyl-substituted alkenes to undergo carboxylation with CO_2 to afford the corresponding α, β-and/or β, γ-unsaturated carboxylic acids.



Scheme 20. *EtAlCl2/2,6-dibromopyridine-promoted carboxylation.*

The authors suggested that zwitterion could be generated via electrophilic addition of starting material to $EtAlCl_2$. Then, 2,6-dibromopyridine would abstract a proton to afford the complex. Carboxylation of the complex affords the aluminium carboxylate. Owing to the far greater acidity of the conjugate acid of the pyridine base (pKa ca2) compared with the carboxylic acid (pKa ca 5), the carboxylic acid could be liberated from the aluminium carboxylate. Apparently, the use of 2,6-dibromopyridine base favours the dissociation of the aluminium–pyridine salt owing to its sterically bulky nature and lower basicity.

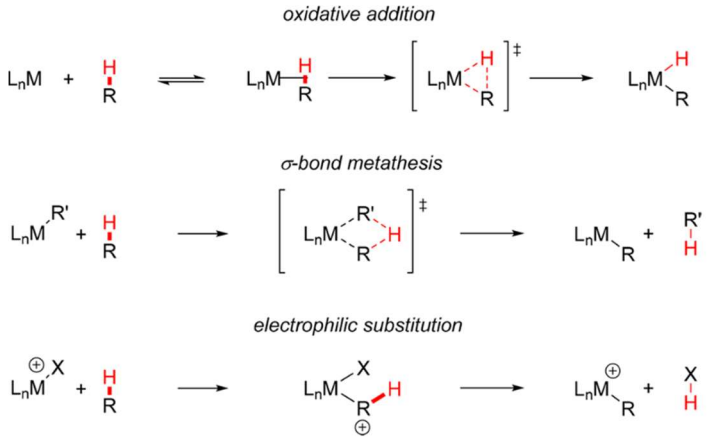


Scheme 21. *Proposed mechanism for EtAlCl2/2,6-dibromopyridine-promoted carboxylation.*

1.3 Group 11 transition metals catalysed carboxylations

During recent decades, transition-metal catalysis has set the stage for efficient direct C-C bond-forming reactions which can proceed under very mild condition. The C-H activation is one of the most effective organometallic techniques which is used for functionalising organic molecule and for making C-C bonds. The organometallic C-H activation consist in functionalising an otherwise inert C-H bond achieving reactivities and selectivities beyond the simple innate substrate control regime.

The elementary step of each organometallic C-H activation is the metalation of the organic site that must be activated. The metalation can be achieved under several conditions depending on the reactivity of the substrate, but It's mostly been proposed to occur by: oxidative addition, σ-bond metathesis or electrophilic activation.



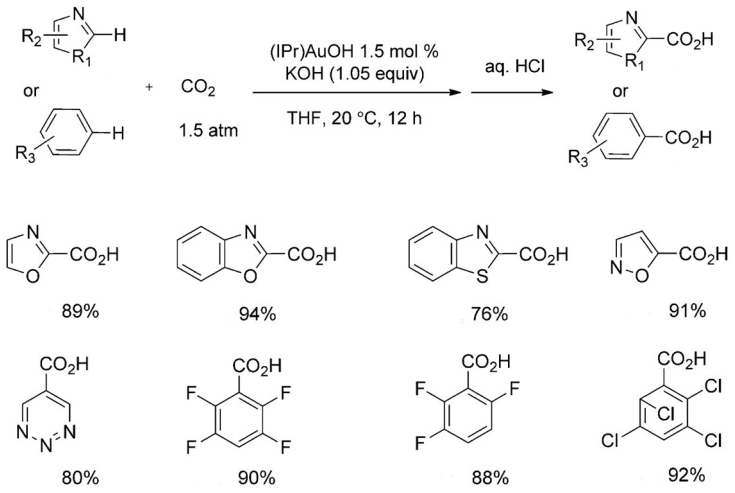
Scheme 22. *Main metalation mechanistic pathways.*

When the C-H bond which is to be activated is partially acidic, the metalation can be achieved using a base. Several examples of transition metals catalyzed C-H carboxylations are reported in literature. Except for Rhodium, all the examples utilize group 11 transition metals, since all these metals can easily metallate acidic C-H bonds in the presence of a base, creating quite stable organometallic species.

Au-catalyzed C-H carboxylation

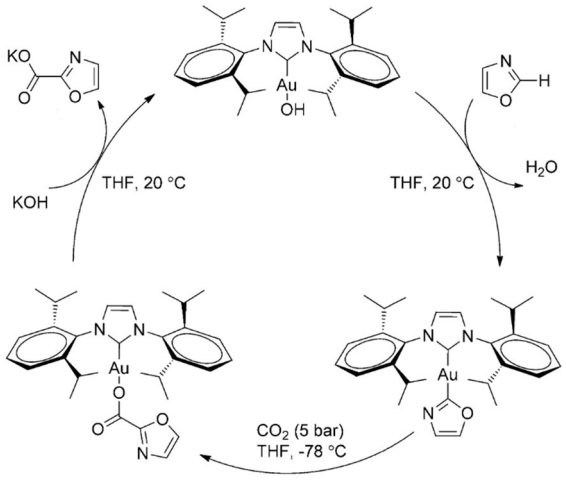
It is proved that linear L-Au(I)Cl complexes can cleave the most electron deficient C-H bond of aromatics to provide the corresponding Aryl-Au(I) species. From this observation a first general protocol was developed for the direct C-H activation of a variety of relatively acidic arenes and heteroarenes with Au(I) complexes through a concerted metalation deprotonation[17]. A wide selection of ligands such as alkyl and aryl phosphines, phosphite, and N-heterocyclic carbenes (NHCs) were found to be compatible with this procedure. Simultaneously, Nolan et al proved that a monomeric, dicoordinate, linear Au(I)/NHC hydroxide complex was able of inducing C-H activation on arenes and heteroarenes [18].

Nolan and co-workers reported that the N-heterocyclic carbene gold hydroxide complexes enabled C-H carboxylation of (hetero)arenes with CO_2 at ambient temperature in the presence of a stoichiometric amount of KOH and only 1.5 atm of CO_2 pressure [19]. The IPr (1,3-bis(2,6-diiso-propylphenyl) imidazol-2-ylidene) gold complex (IPr)AuOH was found to be the most efficient of all examined, leading to the carboxylated products in good-to-high yields. This methodology allowed direct C-H carboxylation of carbocycles and heterocycles including oxazoles, thiazoles, isoxazoles, and some aromatic heterocycles containing multiple heteroatoms. The C-H activation is highly regioselective at the most acidic C-H bond. Additionally, this transformation is efficient for polyfluoro- and polychloro-substituted benzene derivatives.



Scheme 23. *Selected examples of (NHC)AuOH-catalyzed direct C-H carboxylation.*

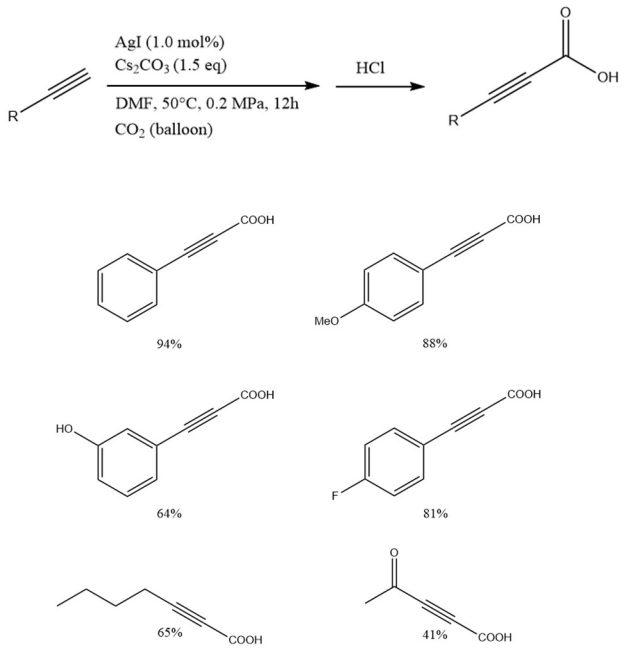
Nolan et al investigated the mechanism of this process carrying out some stoichiometric reactions. By simply mixing gold complex (IPr)AuOH with oxazole, 93% of gold–oxazole specie was obtained. Subsequently, the insertion of CO_2 (5 bar, -78 °C) into the C-Au bond by nucleophilic addition of oxazole to the electrophilic CO_2 carbon atom produced the carboxylate complex in 86% yield.



Scheme 24. *Proposed mechanism for Au-catalyzed C-H carboxylation.*

Ag-catalyzed C-H carboxylation

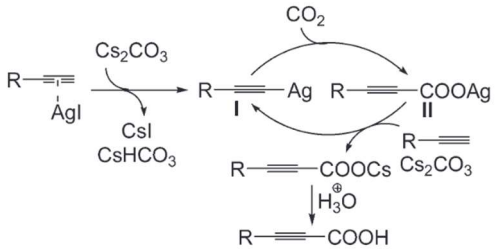
Ligand free silver is reported to be an efficient catalyst for the carboxylation of terminal alkynes. Xiao-Bing Lu and his co-workers developed an efficient carboxylation protocol for terminal alkynes which use a silver salt and $CsCO_3$ as a base at 50°C and 1 atm of CO_2 [20]. The reaction was tested on a wide selection of terminal alkynes using the optimized conditions: 1 mol % of AgI, 1.5 equiv of Cs_2CO_3, 0.2 MPa CO_2, DMF, 50 °C. Both electron-donating and electron-withdrawing group substituted phenylacetylenes were successfully carboxylated with CO_2. The reactions were compatible with aryl-OMe, OH, F, CF_3, Br, Cl, and NO_2 groups.



Scheme 25. *Selected examples of silver salts catalyzed carboxylation.*

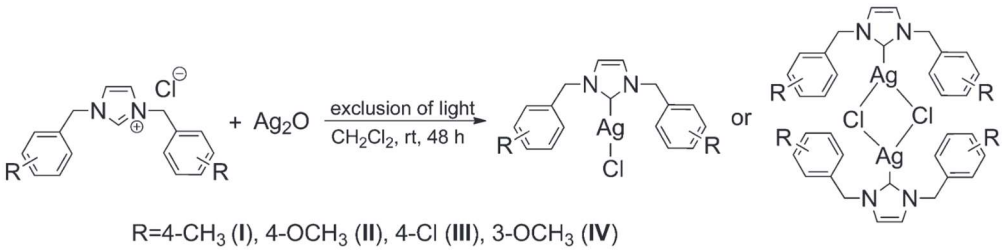
Xian-Bing Lu et al. chosed the phenylacetylene as a trial substrate testing different silver salts as catalyst. The most performing salt were $AgPF_6$ and AgI. Since $AgPF_6$ is highly hygroscopic, AgI was chosed for continuing the tests on the other substrates. Increasing AgI loadings a decreasing in yield was observed, that is explainable by the fact that silver can catalyze the decarboxylation process as well. In addition, the experiments carried on by Hou showed that the choose of the base is very relevant for the succeeding of the catalytic process and Cs_2CO_3 was proved to be the most suitable base.

The mechanistic aspects were investigated, silver phenylacetylide and silver phenylpropiolate were prepared and directly used as catalyst (1 mol %) for the carboxylation of phenylacetylene. It was observed the formation of phenylpropiolic acid with an 80% yield with the acetylide and an 86% yield with the propiolate. Based on the above experimental results, a possible catalytic cycle for the Ag(I)-catalyzed direct carboxylation of terminal alkynes with CO_2 is proposed. First, terminal alkyne coordinates to the silver(I) salt and the acidity of the alkyne C-H bond is enhanced. Then the deprotonation reaction of terminal alkyne by Cs_2CO_3 affords silver(I) acetylide I, which is generally proposed as key intermediate in the silver(I)-catalyzed alkynylation reaction and silver-cocatalyzed Sonogashira reaction. The insertion of CO_2 into sp-hybridized carbon silver bond forms silver propiolate intermediate II, which subsequently reacts with another terminal alkyne and Cs_2CO_3 releasing cesium propiolate, meanwhile regenerating silver(I) acetylide I. The acidification of cesium propiolate after reaction affords propiolic acid product.



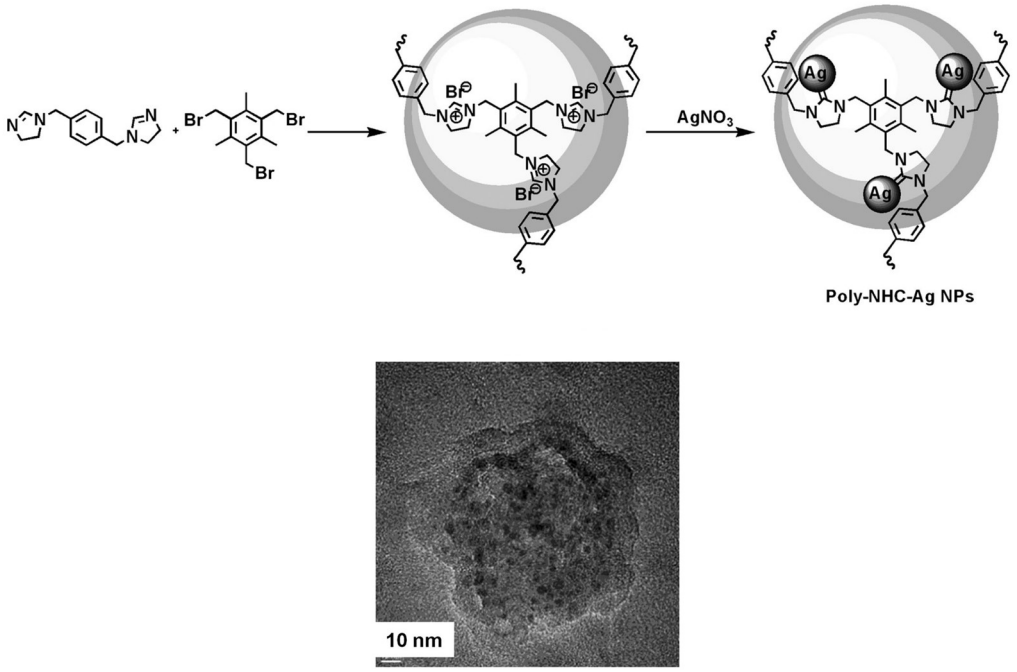
Scheme 26. *Proposed mechanism for silver salts catalyzed carboxylation.*

Zhou and Fang developed a carboxylation process like the one with silver salts using NHC silver complexes (*scheme27*) [21].



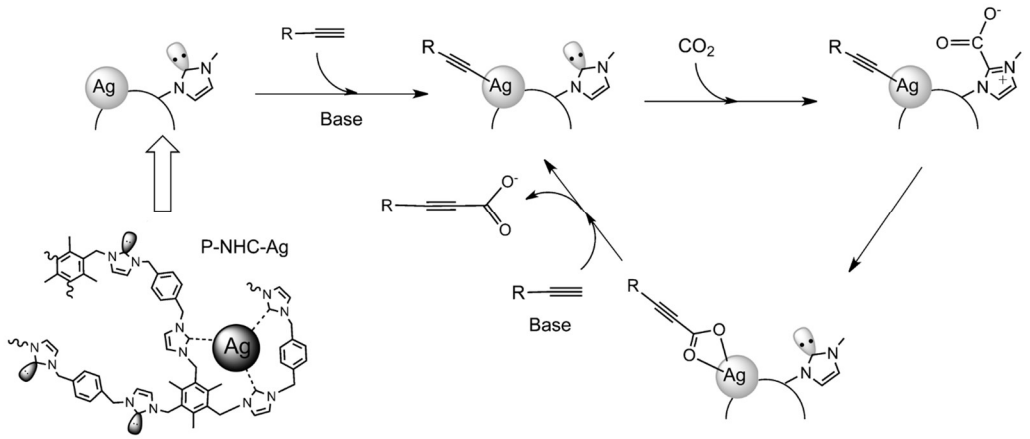
Scheme 27. *Synthesis of Ag–NHCs I–IV Zhou and Fang complexes.*

Tan and Zhang developed a carboxylation process of terminal alkynes catalyzed by poly-NHC-supported silver nanoparticles[22]. This catalytic material was prepared by reacting a poly-imidazolium precursor with $AgNO_3$ in hot dimethyl sulfoxide. Transmission electron microscopy (TEM) was used to show that silver nanoparticles (3–5 nm) were dispersed in a poly-NHC polymer material. The catalyst was firstly tested on phenylacetylene obtaining phenylpropiolic acid (98% yield) with only 0.3 mol% of poly-NHC-Ag catalyst under a CO_2 atmosphere at 20°C in 20 h, using Cs_2CO_3 (1.5 eq) as base and THF as solvent. The catalyst was found not to be sensitive to the functionality of the aromatic alkynes and proved to be tolerant to various functional groups, such as OH, CHO, CN, NO_2.



Scheme 28. *Preparation of poly-NHC-Ag nano-composite and the transmission electron microscopy (TEM) image of the nanocomposite.*

Tan and Zhang stated that the catalytic activity of their poly-NHC-Ag catalytic system can be explained by the synergistic effect between N-heterocyclic carbene polymer and silver nanoparticle. Silver nanoparticles activate the terminal alkyne with the addition of a base to form a silver acetylide intermediate. Meanwhile, the free carbene of poly-NHC activates CO_2 to form an NHC-carboxylate. The NHC-carboxylate then coordinate to a nearby silver center, inducing the nucleophilic carbanion of the alkyne attacking the carboxylic carbon. Following the new C-C bond formation, the carboxylated product get exchanged with the terminal alkyne, restarting the catalytic cycle.

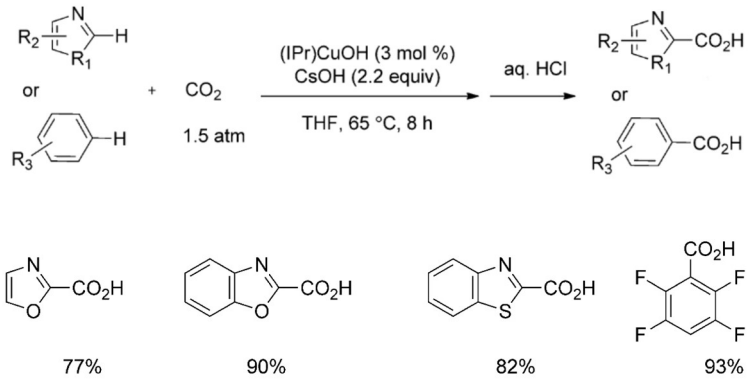


Scheme 29. *Possible reaction mechanism for the poly-NHC-Ag nano-composite catalyzed carboxylation of terminal alkynes with CO_2.*

Cu-catalyzed C-H carboxylation

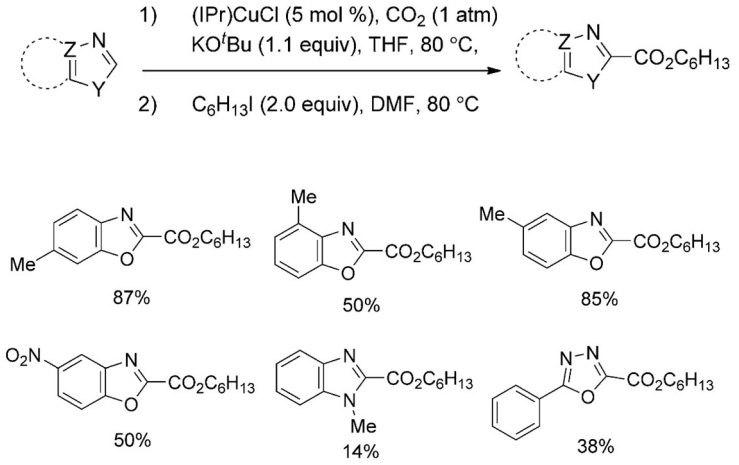
Copper(I) halides are highly active in catalyzing the carboxylation of various aryl and alkyl terminal alkynes with CO_2 in the presence of a strong base under very mild conditions. Consequently, a lot of processes which uses Cu(I) complexes as catalysts are being studying and optimized.

Nolan and his co-workers implemented their methodology using IPrCuOH instead of the corresponding gold complex, managing to carboxylate oxazole, thiazoles and polyflourobenzenes in their most acidic position [23]. This copper-based system permits a significant range of N-H carboxylation (pKa < 27.7) such as imidazole, indole, and pyrazole derivatives.



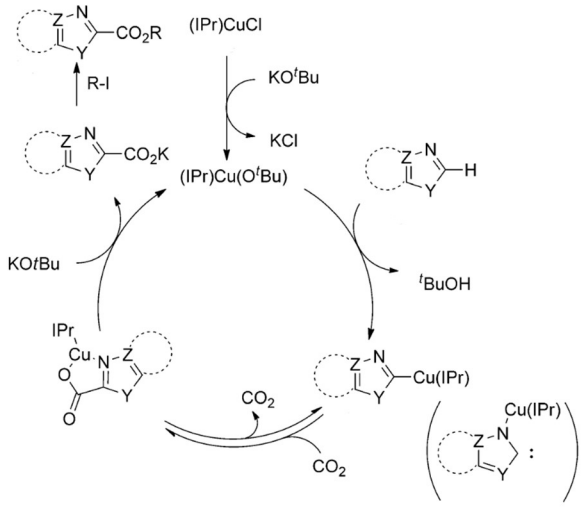
Scheme 29. *Selected examples of (IPr)CuOH-catalyzed direct C-H carboxylation.*

At the same time, Hou and co-workers reported a similar C-H carboxylation using (IPr)CuCl catalyst. They were able to carboxylate, in good-to-high yields under atmospheric CO_2 pressure, benzoxazole derivatives bearing both electron-donating and electron withdrawing groups as the aryl unit. Recently, the authors found that 1,2,3-triazol-5-yidene (tzNHC)-based copper complexes, such as 1,4-di(2,6-diisopropylphenyl)-3-methyl-1,2,3-triazol-5-ylidene-copper chloride (TPr)CuCl could promote the carboxylation reaction somewhat more effectively than the corresponding imidazol-2-ylidene copper(I) complex (IPr)CuCl.



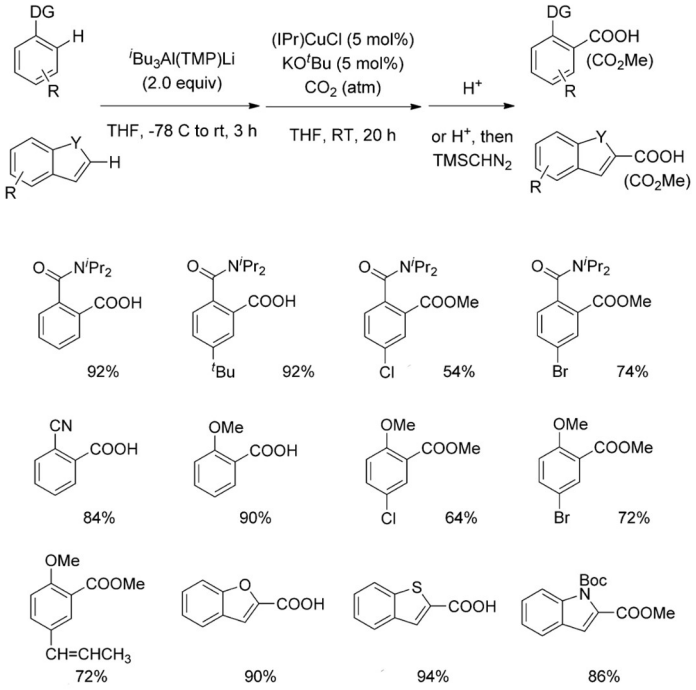
Scheme 30. *Selected examples of (IPr)CuCl-catalyzed direct C-H carboxylation.*

A proposed catalytic cycle is presented in *scheme 31*. Initially, ligand exchange between (IPr)CuCl and KOtBu affords (IPr)Cu(OtBu), which deprotonates the heterocycle metallating the substrate. CO_2 can be inserted to afford a cyclic intermediate which subsequently reacts with KOtBu to regenerate the active specie (IPr)Cu(OtBu) producing the potassium carboxylate. DFT studies carried on by Yates and co-workers suggested an alternative mechanism in which a carbene intermediate is generated in the catalytic cycle, instead of the metallated species. The authors indicated that a carbenic intermediate is more reactive toward CO_2 insertion reaction through nucleophilic attack. Similarly, to the Au-catalyzed direct carboxylation, this method could also be regarded as a C-H deprotonation process.



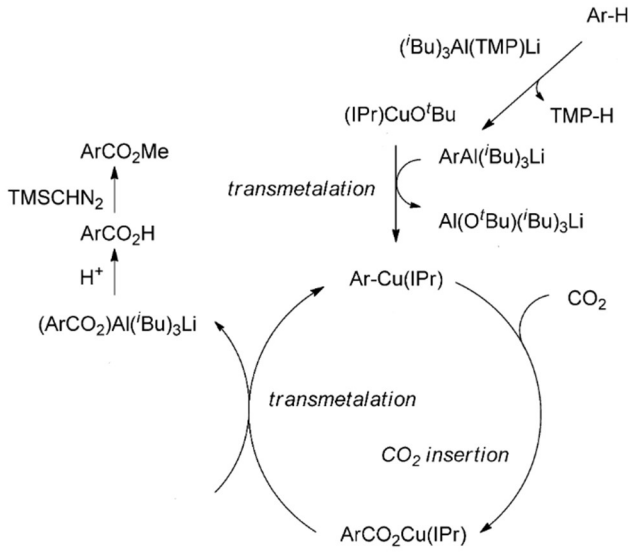
Scheme 31. *Proposed mechanism for (IPr)CuCl-catalyzed C-H carboxylation.*

More recently, Hou and co-workers developed another C-H carboxylation method in which the carboxylated products are afforded by deprotonative alumination using an $iBu_3Al(TMP)Li$ aluminate base [24]. The resulting aryl aluminum species is successively carboxylated with a standard atmospheric CO_2 pressure in the presence of a catalytic amount of an NHC–copper complex and KOtBu. A relatively broad scope of benzene derivatives, such as N,N-diisopropylbenzamide, benzonitrile, and anisole, bearing both electron-withdrawing and electron-donating groups, undergo the alumination/carboxylation sequence to afford the corresponding carboxylic acids in high yield and high selectivity. Heteroarenes such as benzofuran, benzothiophenes, and indole derivatives are also compatible with this method.



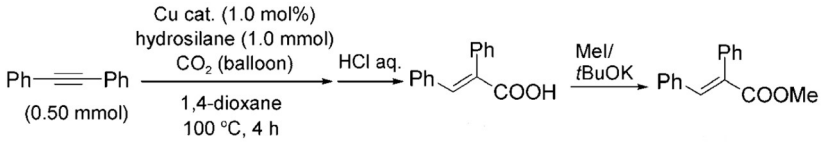
Scheme 32. *Selected examples of Cu-catalyzed formal C-H carboxylation.*

A plausible mechanism is shown in *scheme 33*. Initially, the aryl aluminum specie is generated by deprotonation of the aromatic compound in the presence of aluminate reagent $iBu_3Al(TMP)Li$. The aryl aluminum species then undergoes transmetallation with (IPr)CuOtBu which is formed by treatment of IPrCuCl with KOtBu to give the copper aryl species with release of $Al(OtBu)(iBu)_3Li$. Under CO_2 atmosphere, carbon dioxide is inserted into the Ar-Cu bond of the copper aryl species to give the copper carboxylate complex. Lastly, the transmetallation between the complex and another molecule of the aryl aluminum species gives the aluminum carboxylate specie regenerating arylcopper species. The carboxylic acid is obtained by the hydrolysis of aluminum carboxylate specie, and the ester derivative Ar-COOMe is formed by treatment of carboxylic acid with trimethylsilyldiazomethane ($TMSCHN_2$). This reaction would be classified by the C-H deprotonation-type mechanism.



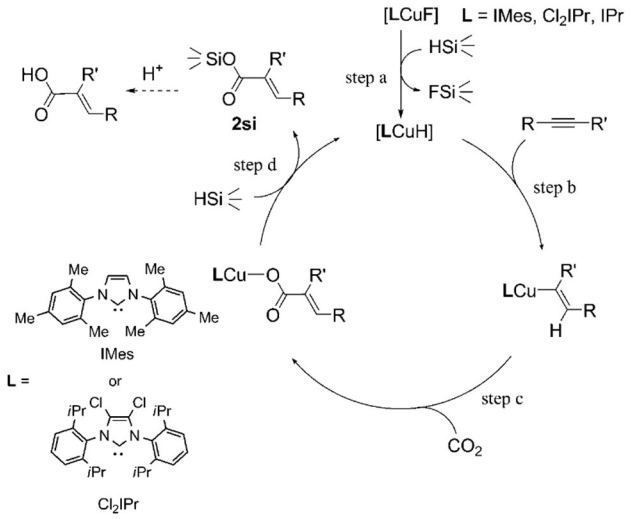
Scheme 33. *Proposed mechanism for Cu-catalyzed formal C-H carboxylation.*

Another interesting prospective given by copper (I)catalysts is the hydrocarboxylation of alkynes. Tsuji et al. were the first to report an hydrocarboxylation protocol of alkynes which uses NHC copper (I) catalysts with the addition of a silane at 100°C in 1,4 dioxane and in CO_2 atmosphere [25]. They optimized their reaction protocol choosing diphenylacetylene as substrate and trying different N-H-C Cu(I) catalysts.



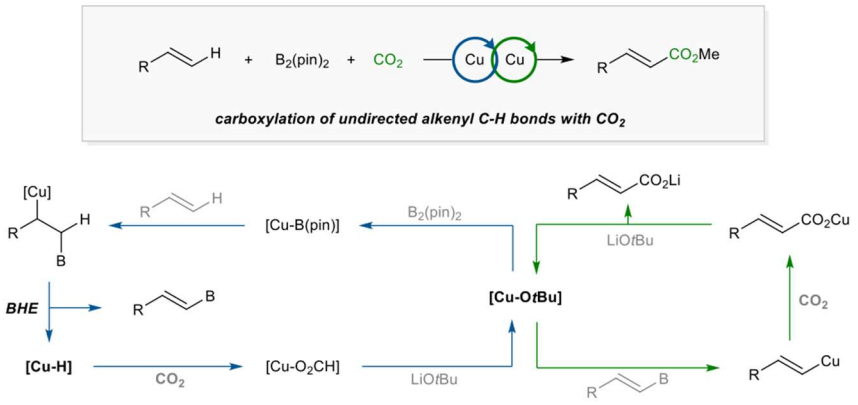
Scheme34. *Hydrocarboxylation of styrene with a copper (I) catalyst.*

The mechanism which was proposed for the reaction start with the activation of the catalyst which happen through the formation of the copper (I) hydride upon reaction with the silane. The catalytically species reacts with the alkyne trough a syn addition reaction which forms stereoselectively a Cu-vinyl intermediate. The insertion of CO_2 can take place on the metal-carbon bond to form the carboxylated intermediate. Finally, a σ metathesis of the carboxylated intermediate with a hydro silane generate the corresponding silyl ester and regenerates the catalytically active species.



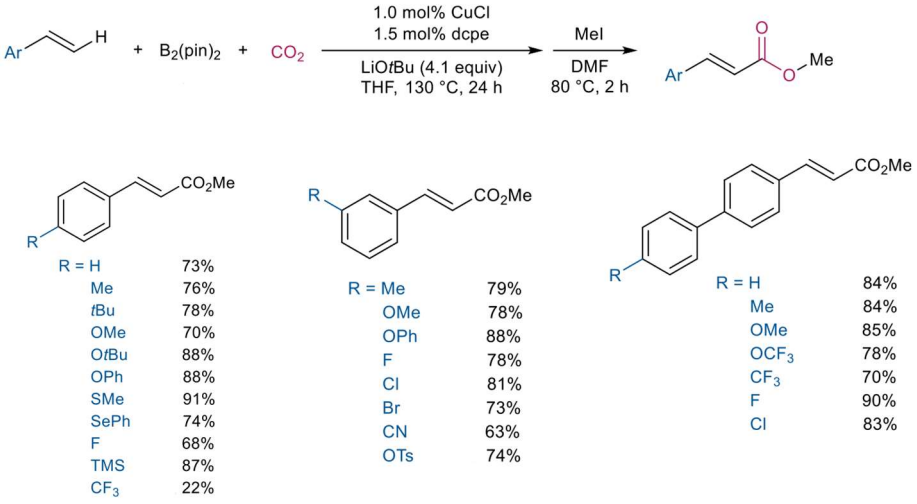
Scheme 35. *Supposed copper (I) catalyzed hydrocarboxylation mechanism.*

More recently, Hou and co-workers developed an interesting hydrocarboxylation process of alkenyl C-H bonds with a copper (I) catalyst which harnesses β-hydride elimination [26]. The particularity of that process is the mechanism, which is an auto-tandem process made up of two different catalytic cycles and one of them harnesses a β-hydride elimination, which is generally considered an unwanted parasite reaction.



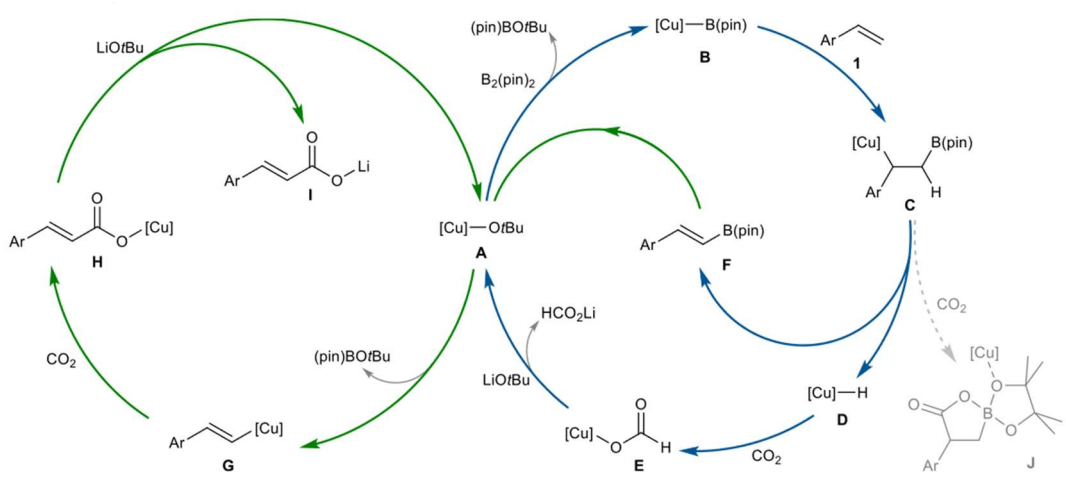
Scheme 36. *Auto-tandem copper catalysis via harnessing β-H elimination*

They decided not to use a pre-assembled catalyst but to add directly the metallic center and the ligand with the addition of a base using THF as solvent. The optimization of the process took place using styrene as a trial substrate, different temperatures and high catalyst loadings (10% mol of CuCl and 15%mol of ligand) but It is noteworthy to highlight that the reaction can proceed with a 1mol% of catalyst without erosion of the yield. The optimization process found out that among a series of electron-rich phosphine ligands dcpe remains the best choice. The yield of the desired product increases with the temperature, which induced to choose 130°C as optimized temperature.



Scheme 37. *Selected examples of auto-tandem copper catalyzed hydrocarboxylations*

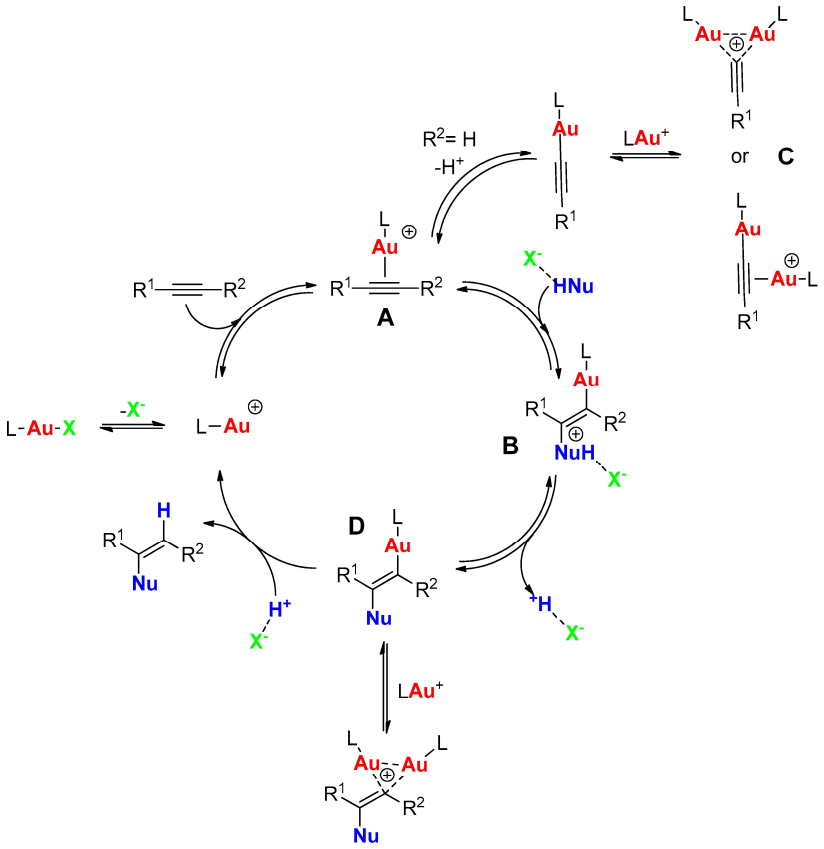
A possible reaction mechanism was proposed. The initial metathesis reaction between the copper chloride catalyst precursor and LiOtBu affords copper tert-butoxide **A**, which upon reaction with $B_2(pin)_2$ generates the boryl copper complex **B**. The subsequent regioselective insertion of the C−C double bond of the alkene substrate **1** into the Cu−B bond of **B** give the β- borylalkyl copper species **C**. Although the insertion of CO_2 into the Cu−C bond in **C** to generate a bora carboxylation intermediate could take place, our current catalytic system significantly accelerates β-hydride elimination of **C**, affording copper hydride **D** along with alkenyl boronic ester **F**. In the absence of CO_2, a following reinsertion process could give the corresponding rearranged α-borylalkyl complex. However, in the current system, copper hydride **D** instantaneously reacts with CO_2, resulting in the formation of copper formate E, which upon reaction with LiOtBu releases lithium formate and regenerates the key active species **A**. Subsequently, the reaction of alkenyl boronic ester **F** with the Lewis basic intermediate **A** results in transmetallation of the alkenyl group to the copper center and generate an alkenyl copper complex **G**, which reacts with CO_2 to give then copper acrylate intermediate **H**. Finally, metathesis between LiOtBu and H affords the lithium acrylate I and regenerates copper tert-butoxide **A**. Treatment of the lithium salt **I** with methyl iodide yields the methyl acrylate product.



Scheme 38. *Proposed reaction mechanism for the auto tandem copper catalyzed hydrocarboxylation.*

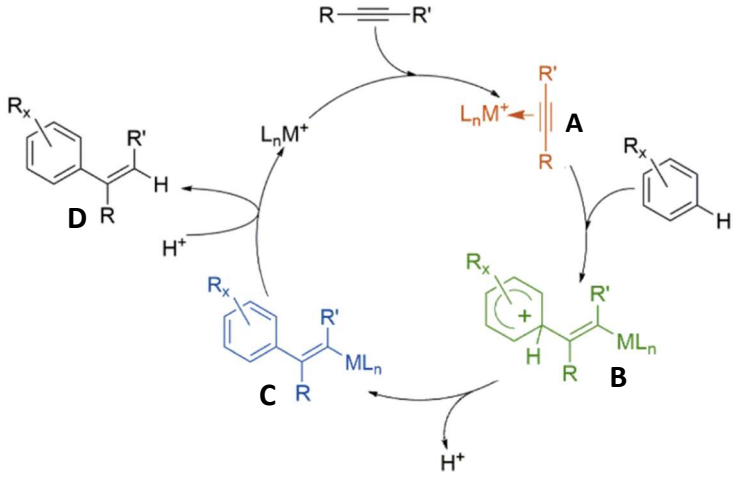
1.3 Gold catalyzed hydroarylation of alkynes

In order to understand the main goal of the thesis is necessary to introduce the essential theory behind gold catalyzed hydrofunctionalization of alkynes. As shown in the chapter on gold catalyzed C-H carboxylation, gold can metallate compounds with acidic C-H bonds, such as (hetero)arenes and alkynes. On the other hand, gold complexes are also strongly carbophilic, in that they are soft lewis acids that coordinate strongly to unsaturated organic molecules through their π-system; in doing so, they activate those systems towards external nucleophilic attack. In particular, the alkynophilicity of Au(I) complexes has indeed become a powerful tool for the activation of such compounds toward different nucleophiles, including aromatic organic molecules. Generally, gold catalyzed hydrofunctionalizations are carried out with electron-rich arenes or heteroarenes and electron-poor alkynes giving rise to disubstituted alkenes with good conversions and yields. The first complexes which were employed were of Pd (II) and Pt (II) with the addition of a strong Lewis or Brønsted acid as cocatalyst. The Pd-catalysed hydroarilation reaction is also termed Fujiwara reaction. Lately, other electrophilic Lewis acids and carbophilic transition metals were successfully employed as catalysts for this reaction, showing interesting activities and selectivities and different mechanisms too. Gold proved to be the most suitable metal since its unique alkynophilicity behaviour that can be used to efficiently run hydroarylations under mild conditions with low catalyst loadings. Keeping the focus on intermolecular alkyne functionalization by protic nucleophiles HNu, the reaction mechanism of a gold-catalyzed direct alkyne hydrofunctionalization reaction can be typically reduced to the one reported in *scheme 39*. [27]



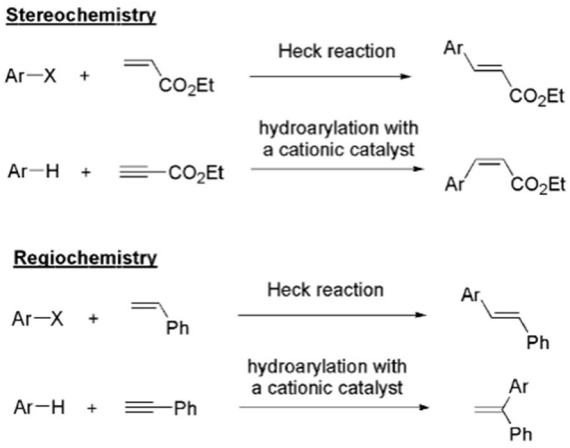
Scheme 39. *General mechanism for cationic gold(I)-catalyzed alkynes hydrofunctionalization. Taken from reference* [27]

Hydroarylations are a particular type of hydrofunctionalizations in which an Ar-H or (HetAr)-H is added to a triple C-C bond with the subsequent formation of an aryl alkene. This synthetic approach is stereoselective for the anti-addition product and it allows to directly react alkynes and arenes affording a new C-C bond without the use of prefunctionalized starting materials. Several examples of intramolecular and intermolecular hydroarylation of alkynes have been developed. The reaction follow a Friedel-Crafts mechanism (*scheme 40)*: a cationic, ligand stabilized complex of gold(I) activates the alkyne by π-coordination (**A**) which is now prone to an electrophilically attack on the arene yielding a Wheland-type intermediate (**B**), whose proton can be removed by any basic species present in the reaction mixture restoring the aromaticity of the ring and providing the metal-vinyl intermediate (**C**). The latter is then subject to the protonolysis step giving rise to the hydroarylation product (**D**) and regenerating the catalytic competent species. Essentially, in the hydroarylation reaction a C(sp2)-H bond is cleaved, and the hydrogen atom is substituted with a vinyl moiety giving rise to disubstituted alkenes. As shown in the catalytic cycle above, the product is a Z-olefin.



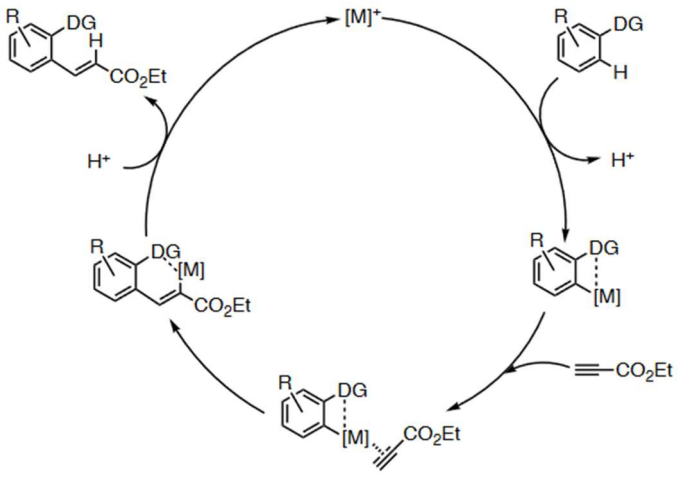
Scheme 40. *Friedel-Crafts mechanism of the alkyne hydroarylation reaction.*

Depending on the nature of the R group of the alkyne, different regioselectivities can be achieved. The mode of the addition is trans, whereas the regiochemistry is controlled by the electronic nature of the substituent on the triple bond. Generally, intermolecular hydroarylation of terminal alkynes leads to 1,1-disubstituted alkenes, because of a complete Markovnikov regiochemistry. However, alkynes with electron withdrawing groups afford 1,2-disubstituted derivatives, hence satisfying the anti-Markovnikov rule[28].Therefore, this reaction appears to be complementary to the more traditional Heck reaction between aryl halides and electron-poor monosubstituted olefins, which usually delivers E-arylalkynes[29] (*scheme 41*). Moreover, steric hinderance at the arene is not limiting the reaction, which is driven by the electronic properties of the substrates rather than steric effects which is again in contrast with the Heck reaction.



Scheme 41. Comparison of stereo- and regioselectivity between Heck and hydroarylation.

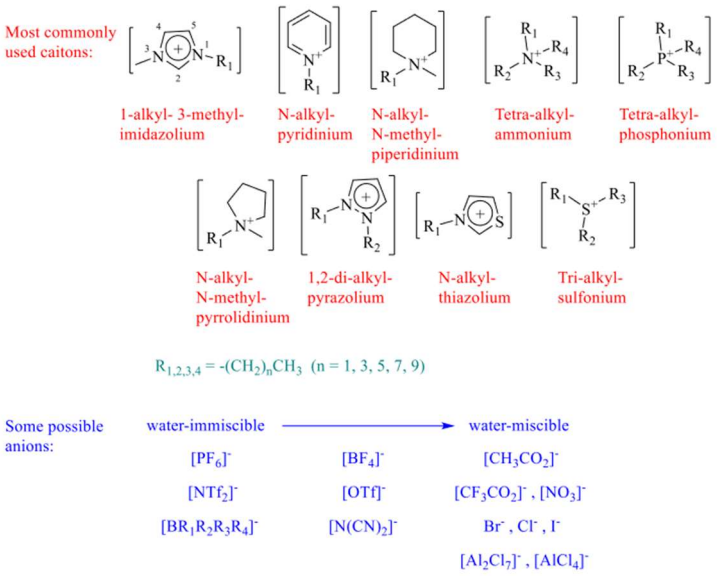
Other less electrophilic complexes of metals such as ruthenium, rhodium, nickel and cobalt where employed as catalysts for alkyne hydroarylation reactions [30]. With these catalysts, the reaction mechanism is generally considered to be different and it involves initial arene metalation (*scheme 42*). The arene metalation is followed by alkyne coordination, insertion into the metal-arene bond and final protonolysis of the resulting metal-vinyl intermediate. The metalation step is critical and a directing group on the arene substrate is often required for the reaction to proceed at a synthetically useful rate. Nevertheless, the activity of these catalytic systems is often quite low and the stereoselectivity of the reaction is often poorly controlled.



Scheme 42. Alternative hydroarylation reaction mechanism.

1.5 Ionic Liquids as reaction media for hydroarylations

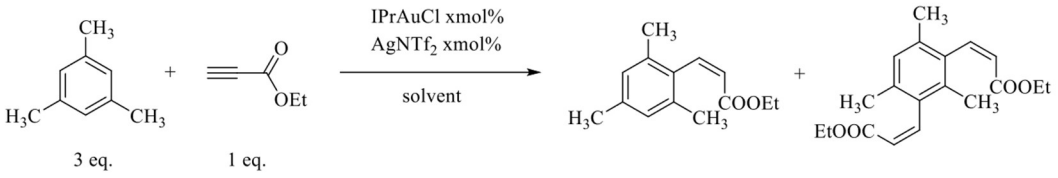
The term ionic liquids is referred only to salts with melting temperature under 100°C. They can be liquid even at room temperature, colourless and poorly viscous. The chemical nature of these species is broad and the cation or anion moiety can be chosen independently. In *scheme 43* are reported examples of some common cations and anions which are employed in ionic liquids.



Scheme 43. *Chemical nature of cations and anions in ionic liquids.*

Ionic liquids can be considered as eco-friendly alternatives to the traditional organic solvents since they can solubilize a wide variety of organic, inorganic and polymeric species. Their most important feature is their tunability to the processes in which they are used, since their physical and chemical properties can be modified with the choice of their cations and anions and there is a broad amount of species that can be chosen. Ionic liquids can act as catalytically active species, or they may represent the solvent for a transition metal catalyst forming a catalytically active ionic solution. Different works conducted on alkyne hydroarilation in ionic liquids showed that ionic liquids improve the catalyst activity [30]. Indeed, selected ionic liquids can promote the dissociation of anionic ligands with the formation of cationic catalytic metal species, stabilize the cationic intermediates of the reaction and promote proton transfers, lowering the energy barrier to overcome the protonolysis step and afford the hydroarylation product.

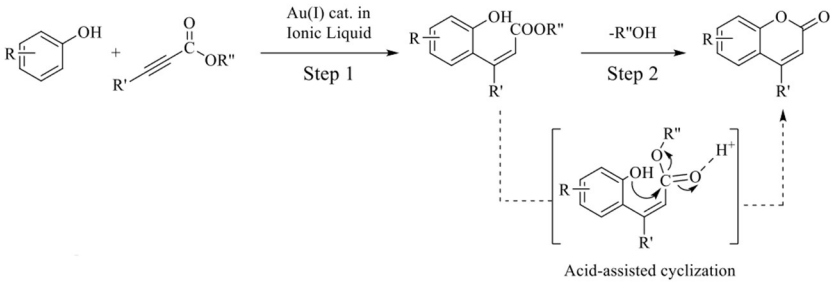
In alkyne hydroarylations using group 13 and early-transition metal salts as catalysts, ionic liquids were found to drastically improve their performance [31-33]. For example, hydroarylation of 1-phenylprop-1-yne with benzene in the presence of 10 mol% Sc(OTf)3 in 1-butyl-3-methylimidazolium hexafluoroantimonate ([BMIM][SbF6]) is complete within 4 hours affording 1,1-diphenylprop-1-ene in an excellent yield, whereas without use of the ionic liquid the reaction provides a low yield (27%) of the product after 96 hours [32]. Biffis and co workers reported an improved performance in the case of the hydroarylation of ethyl propiolate with mesitylene catalyzed by IPrAuCl/AgNTf [34]. (*scheme 44*)



Conditions	Alkyne conversion	Mono-/Di-hydroarylation products molar ratio
BMIM NTf_2, 0.5 mol% cat. , 3h	> 90 %	5 : 1
$(CH_2)_2Cl_2$, 60°C , 5 mol% cat. , 4h	> 90 %	2 : 1

Scheme44. *Effect of the IL medium on propiolic acid hydroarylation with mesitylene.*

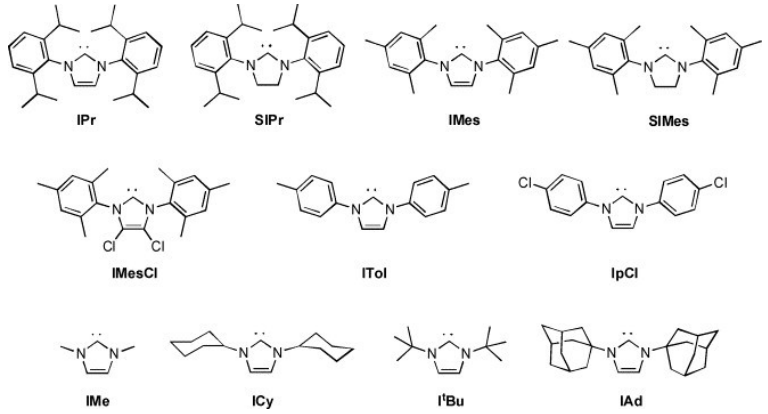
The hydroarylation is reported to be much more efficient in BMIM NTf2, achieving more than 90% of alkyne conversion and improved selectivity toward the single adduct formation. To have a comparable result in DCE as solvent, the catalyst loading has to be increased from 0.5 to 5 mol% with longer reaction times and at higher temperature. The hydroarylation reaction developed and optimized by Biffis and co-workers was employed for designing a one-pot synthesis of coumarines which is taken in consideration in the work of this thesis[35].



Scheme45. *Direct synthesis of coumarines by alkynes intermolecular hydroarylation in ILs.*

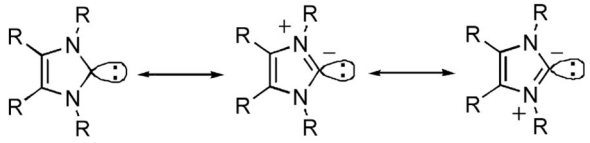
1.4 N-heterocyclic carbene (NHC) ligands

Since all the metallic complexes synthetized and tested in this thesis contains NHC ligands, it is important to introduce some historical and theoretical aspects regarding this class of ligands. It has to be mentioned that they have just started recently to catch an increasing attention. Initially, they were considered just as phosphines ligand mimic [36], but with time they proved to surpass their phosphine-based counterparts in both activity and scope[37-43]. Despite the existence of several families of stable carbenes, only the five-membered cyclic diamino carbenes have found numerous applications as ligand so far. Even if exceptions have been reported [44], free acyclic carbenes including diamino carbenes [45-47] are far more fragile than these NHCs and they are poorer ligands, so far, for transition metal complexes [48].



***Scheme 46**: NHC carbenes which are most used as ligands.*

All the theoretical and experimental evidence indicates that to form a stable carbene the carbenic carbon must be bonded to strong π-donor atoms [49,50]. For this reason, the discovery of the first isolated carbene seemed so unexpected. Recent studies showed the unexpected stability of free NHC arise mainly from substantial charge transfer from the carbenic carbon to the more electronegative neighbouring nitrogen. Further computational studies postulate that the p(π)–p(π) delocalization is not extensive and that the bonding in these ligands should be considered carbenic since ylidic resonance structures are not dominant contributors [51]. Similar conclusions have been reached using different techniques [52-54]. Therefore, π - donation would only play a minor role.

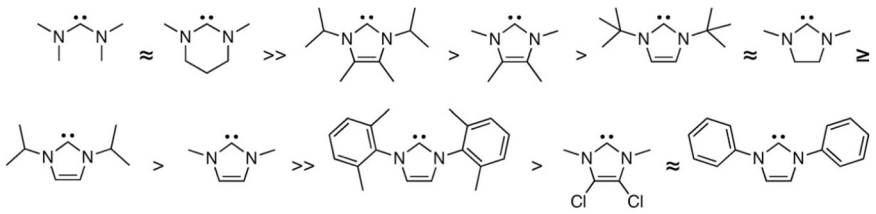


***Scheme 47.** Ylidic resonance structures of a generic NHC carbene.*

Recently, it has been argued that the dominant factor which stabilize the carbenes is the donation from the nitrogen lone pairs into the formally empty p(π) orbital of the carbene carbon atom [55, 56]. These authors also showed that the method of density mapping employed by Arduengo was not suitable for analysing electron delocalization. Their theoretical and experimental reports have also suggested that there is a cyclic electron stabilization, conferring the imidazol-2-ylidenes a certain aromatic character [57]. This aromaticity would be appreciably smaller than in benzene or imidazolium salts but still significant from magnetic and thermodynamic perspectives. The classical explanation invoking a thermodynamic stabilization of the carbenes via cyclic 6 p(π) -electron delocalization had to be reviewed after the isolation of the first

imidazolin-2-ylidenes in 1995 [58]. It was then clear that such a delocalization would only be an additional stabilizing factor, and that the electron donation of the nitrogen atoms would be necessary and sufficient for stabilizing the free carbene.

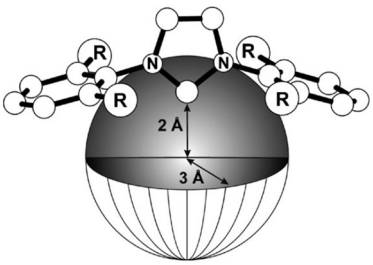
The overall availability of the carbene lone pair is dependent of a combination of electronic and steric properties of the ligand in a specific coordination environment [59]. The availability of the lone pair is obviously correlated to the basicity. Recent theoretical studies have allowed a classification of the most used carbenes according to their basicity [60]. This study proved that the most important factor which determine the basicity is the NCN angle while electron delocalization is not so relevant.



Scheme 48. *NHC carbenes ordered following their basicity.*

An empirical approach for understanding the electronic properties of these ligands is based on the study of the carbonyl stretching frequencies of NHC-containing carbonyl transition metal complexes. These studies states that NHCs are more electron-donating than phosphines which is explained by the fact that NHCs are better σ-donor than even the very basic phosphine, P^tBu_3 [61-63]. In addition, they suggest that saturated NHC ligands would be slightly less electro-donating than their unsaturated analogues and that alkyl-substituted NHCs are only marginally more electron-donating than their aryl-substituted counterparts. However, it should be considered that no studies on the basicity of late generation phosphines, that have shown enhanced catalytic activities, have been reported to date.

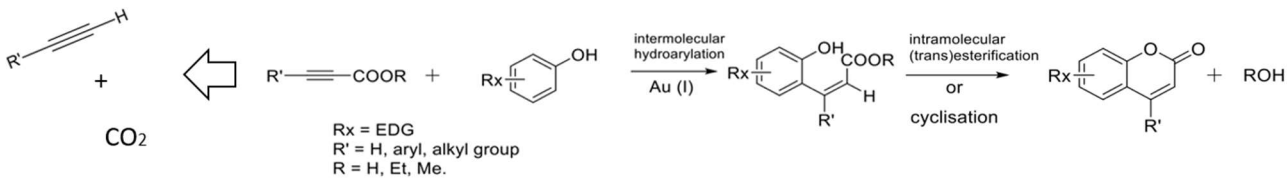
The steric effects are quantified trough crystallographic models and modelist approaches. From structural studies It can only be concluded that bulkiness of the groups bound to the nitrogen atoms of the NHC ligands and more importantly, the short metal–carbon distances in these complexes, increase the steric congestion around the metal center when compared to tertiary phosphines. The model which quantifies the steric requirements of these ligands considers the percent of the volume occupied by ligand atoms in a sphere centered on the metal ($\%V_{Bur}$)[43].



Scheme 49. *Representation of the sphere dimensions for steric parameter determination (%VBur) of NHC ligands.*

2. AIM OF THE THESIS

The *Applied Organometallic Chemistry* group (DiSC-UNIPD, Prof. Biffis) had already developed and optimized an efficient protocol for Au (I) catalyzed hydroarylations to produce coumarines from alkynes and phenols [35]. The first purpose of this thesis was to design and optimize a protocol for a C-H carboxylation combined with Au catalyzed hydroarylation to build up a one pot process for the synthesis of coumarines which could start from the simplest substrates possible. The idea seemed promising since the same gold catalyst used for hydroarylation and the silver salt which is used as catalyst activator are supposed to be able to catalyze C-H carboxylations. Moreover, the gold(I) catalyst is unable to promote the hydroarylation of terminal alkynes that do not present electron-withdrawing groups, hence the hydroarylation reaction will only proceed on the carboxylated alkyne [19]. Naively, it can seem a simple idea, but it is not, since all transition metals which catalyze carboxylations work with the presence of a base, whereas the hydroarylation needs a Lewis acid to work. Initially, the research focused on understanding how to perform the hydroarylation process in presence of a base and on the reproduction of literature data on gold and silver catalysed carboxylations. Later, the research focused mainly on hydrocarboxylations and copper(I) and (II) catalysts which should be able to catalyze those processes.

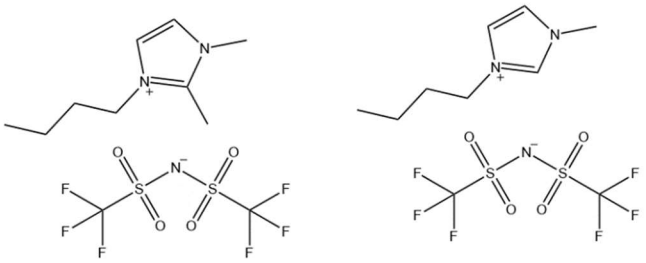


Scheme 50. *Au catalyzed hydroarylation process for coumarin synthesis and retrosynthetic production of the propiolic substrate through carboxylation of a terminal alkyne.*

3. RESULTS AND DISCUSSIONS

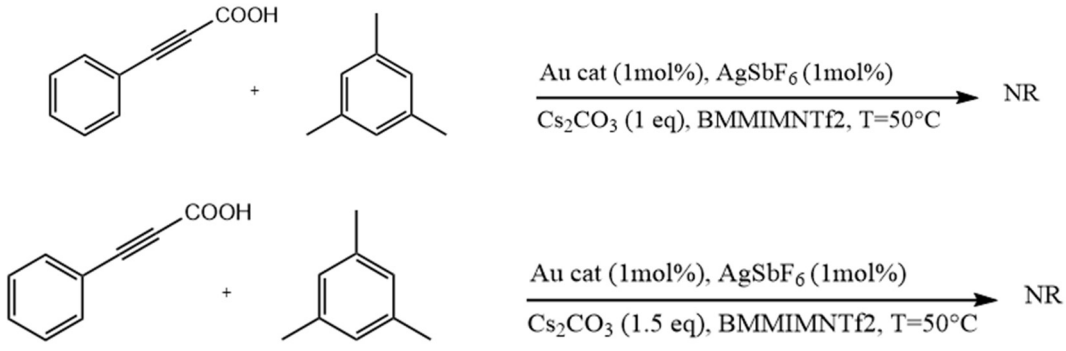
3.1 Au catalysed hydroarylation in presence of a base

The first focus of the research was about the possibility of performing an Au catalyzed direct alkyne hydroarylation in the presence of a base. This was essential to be verified since the vast majority of metal catalyzed C-H carboxylation protocols involve the use of a base. To pursue this purpose some hydroarylation tests were performed following the optimized protocol which requires 1mol% catalyst loading and 1mol % $AgSbF_6$ as activator in ionic liquid as solvent at 50°C. The ionic liquid which was chosen for performing these tests was 1-butyl-2,3-dimethylimidazolium bis (trifluoromethyl sulfonyl) imide $BMMIMNTf_2$, which is the same optimized ionic liquid for the reaction BMIMNTf2, except for a methyl in position 2 in the imidazolic ring. This choice was made to avoid the possibility that the carbonate ion could deprotonate the imidazolic proton of the cation $BMIM^+$ for being successively metallated by the gold catalyst instead of the substrate. This choice is not supposed to generate reactivity issues since the hydroarylation in $BMMIMNTf_2$ is proved to exhibit similar catalytic performances than in $BMIMNTf_2$ [35].



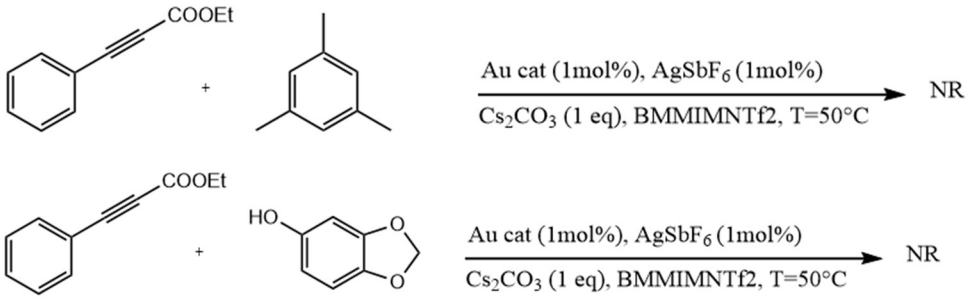
Scheme 51. Respectively from right to left $BMMIM^+NTf_2^-$ and $BMIM^+NTf_2^-$

The substrates which were firstly chosen for performing the tests were mesitylene and phenylpropiolic acid, using Cs_2CO_3 as base since it is the most efficient for carboxylations processes. The first tests were carried on with 1.5eq and 1eq of $CsCO_3$ without observing any trace of the attended product (*scheme 52*).



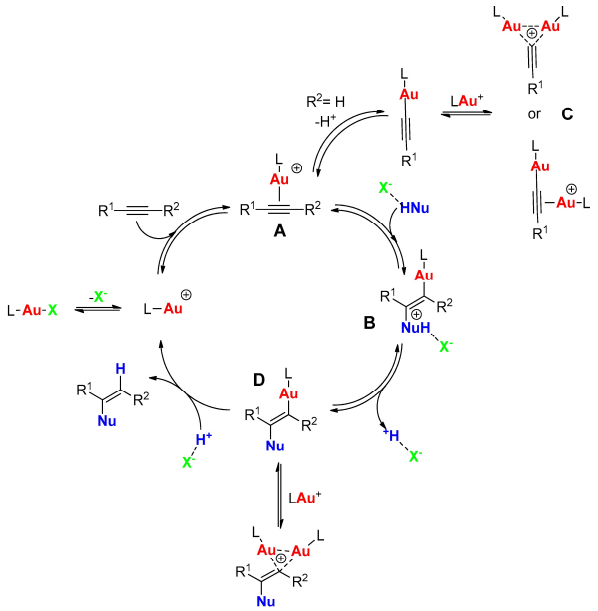
Scheme 52. Hydroarylation of the phenylpropiolic acid with mesitylene adding respectively 1 and 1.5 eq of Cs_2CO_3 as base

Observing the ^{1}HNMR spectra of the reaction crudes, phenylpropiolic acid was not detected which means that its deprotonated form was likely not to be soluble in the ionic liquid. This fact suggested that it was better to carry out additional tests with ethyl phenylpropiolate instead of phenylpropiolic acid and 1eq of base. In addition, another test with the sesamol instead of the mesitylene and 1eq of base was done. Both tests did not provide the attended products.



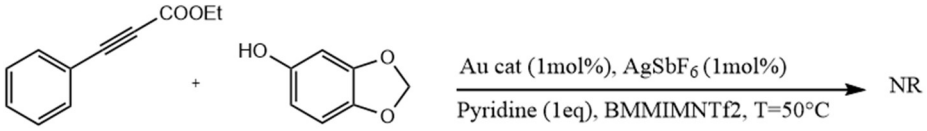
Scheme53. Hydroarylation of ethyl phenylpropiolate with mesitylene and sesamol adding 1 eq of Cs_2CO_3 as base.

Basing on these results is clear that an inorganic and not reversible base is not suitable for the hydroarylation process. The reason of this lack of reactivity is not likely to be the consequence of catalyst deactivation, because the carbonates anion interacts weakly with the gold centre of the catalyst, so they should not be able to deactivate it. The reason is most likely to concern the lack of protons available in solution for the protodemetallation step and the difficulty in moving them in a such basic environment. Looking at the general hydroarylation mechanism reported in *scheme 54*, it can be noticed that the interconversion of **A** to **B** and **B** to **D** requires proton shuttling, which become very slow and inefficient in basic conditions. In addition, the final and irreversible step which affords the hydroarylation product is a protonolysis and it is not supposed to happen in basic condition. Starting from these first results and considerations, the possibility was evaluated of trying to perform the hydroarylation in the presence of some organic and reversible bases, which could have made the basic conditions less extreme preserving the proton mobility in the reaction medium.



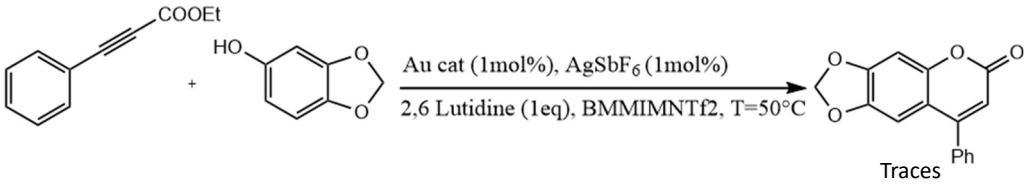
Scheme 54. *Au catalyzed hydrofunctionalization mechanism.*

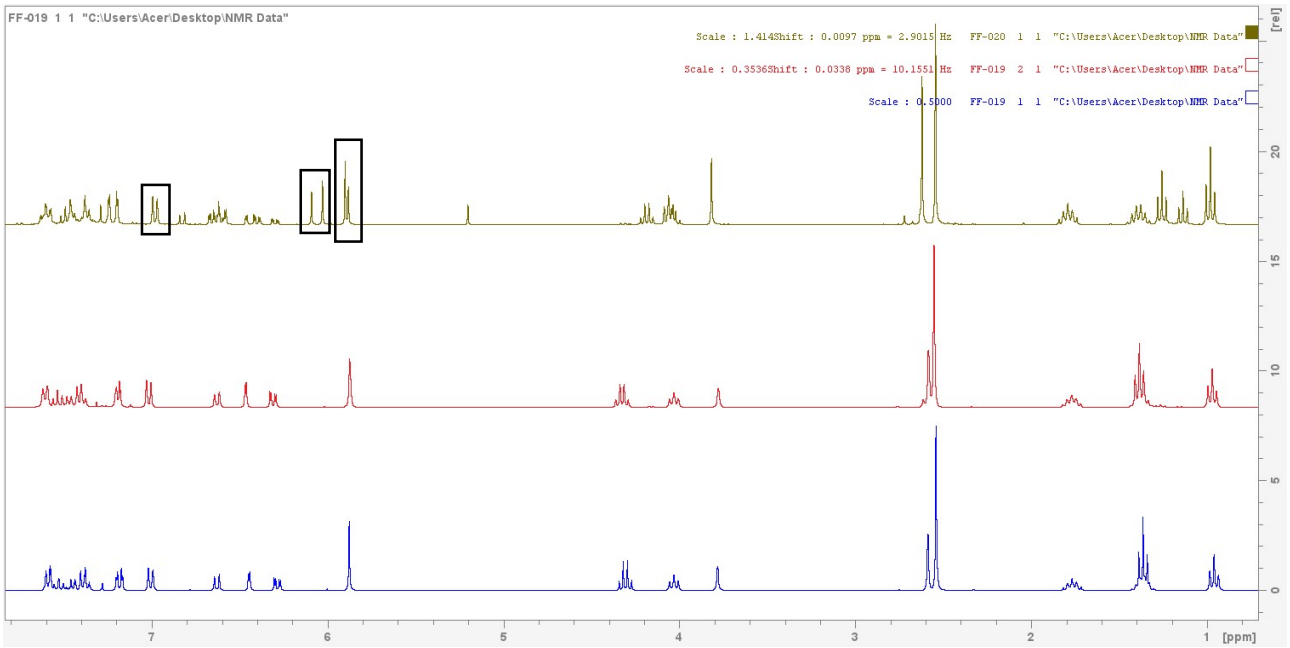
Consequently, it was chosen to perform two other tests in the same conditions, using pyridine as base but without obtaining any trace of the expected hydroarylation product. In that case, it is possible that the reason of the failure was not due to the lack of protons in the reaction environment but to the ability of the pyridine to coordinate with the gold centre of the catalyst deactivating it towards the hydroarylation.



Scheme 55. *Hydroarylation of ethyl phenylpropiolate with mesitylene adding 1eq of pyridine as base.*

In order to verify this assumption another catalytic test was performed using the 2,6 lutidine as base. 2,6 Lutidine is a pyridine substituted in the position 2 and 6 of the ring which makes it a less coordinating base Lewis base than a non-substituted pyridine, despite its slightly stronger Brønsted basicity, due to its greater steric hinderance. The catalytic test performed with 2,6 lutidine as base provided the attended product in traces (yield<5%) verifying the assumption. The outcome of this experiment proves that the hydroarylation process can work in specific basic conditions as well even if not in the same efficient way as under neutral or even acidic conditions.



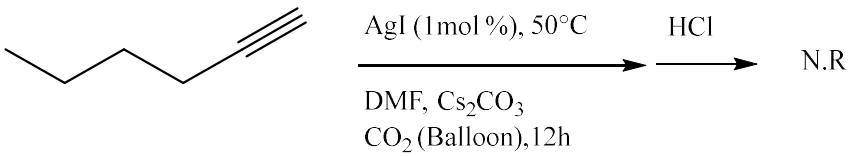


Scheme 56. *Hydroarylation of the ethyl phenylpropiolate with sesamol adding 1 eq of 2,6 lutidine as base and ^{1}H NMR (300 MHz, $CDCl_3$) of the reaction crude at time* ***0h*** *(blue line), at* ***3h*** *(red line) and at* ***24h*** *(green line). The most diagnostic signal is the shift of the methylenic protons to higher chemical shift, the diagnostic signals of the produced coumarine are evidenced in black squares.*

3.2 C-H carboxylation with silver salts

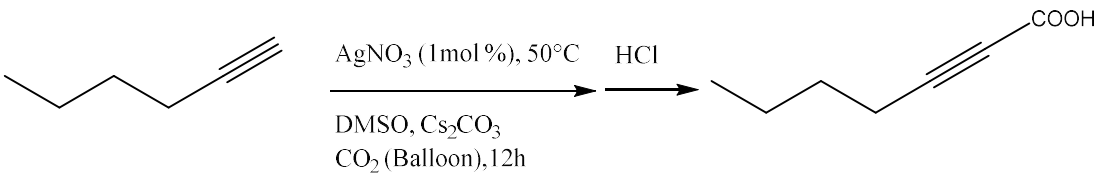
The first steps made for studying the carboxylations processes were to try to reproduce silver salts catalysed carboxylations. The possibility of using a silver salt for catalysing the C-H carboxylation of alkynes is very appealing since they are cheap and readily available. Furthermore, silver salts are used to activate gold(I) complexes as catalysts for the direct alkyne hydroarylation reaction, hence there is in principle the possibility to employ a single silver salt additive for both purposes, alkyne carboxylation and activation of the gold(I) catalyst for subsequent hydroarylation.

Two carboxylation trials were performed using 1-exyne as substrate, basing on a literature procedure [20]. The first trial was carried on in anhydrous DMF using AgI as catalyst (loading 1mol%), but it did not provide any result.

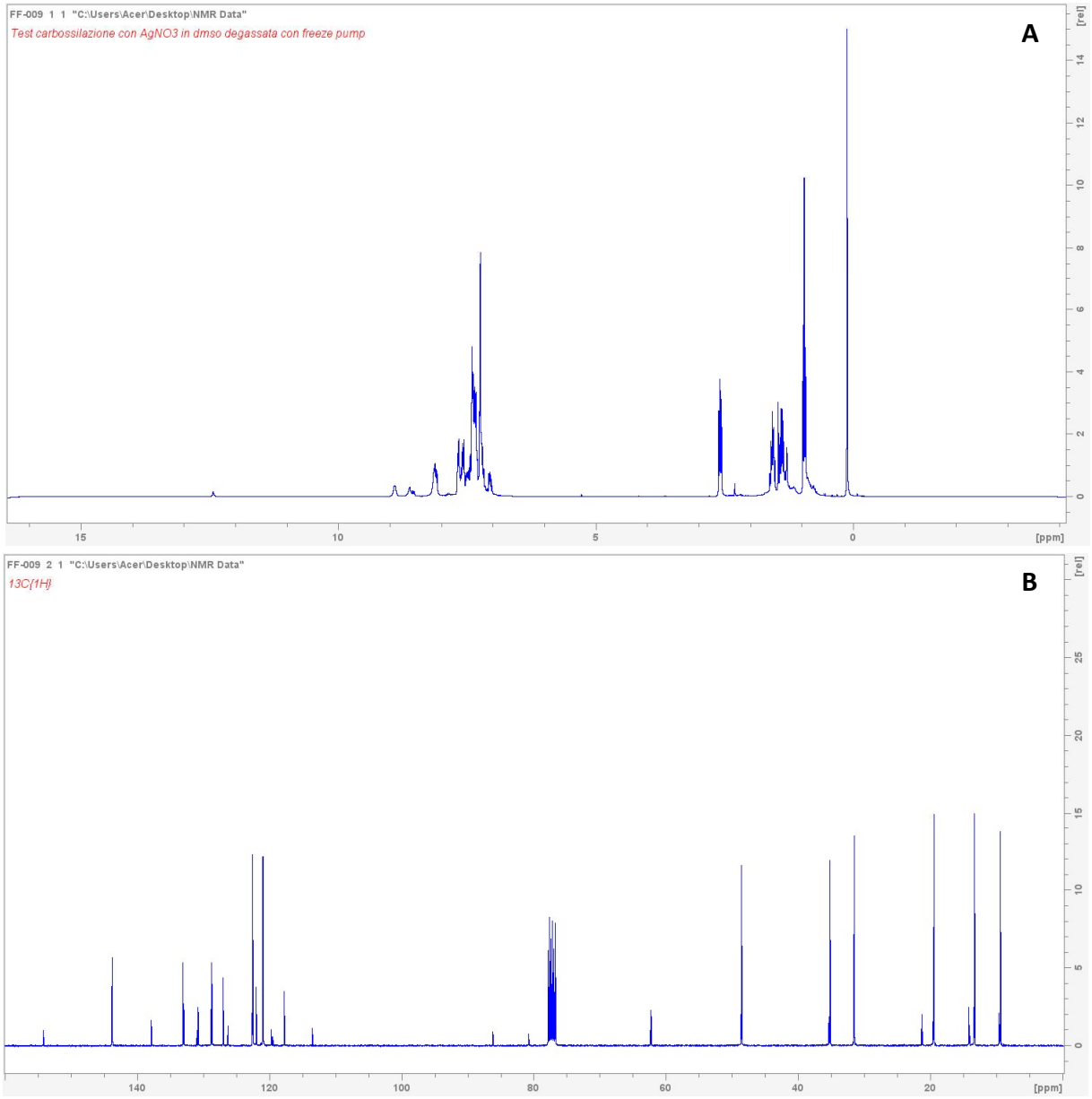


Scheme 57. *Silver catalyzed carboxylation of 1-hexyne with AgI in DMF.*

The second trial was carried on using DMSO as solvent and anhydrous $AgNO_3$ as catalyst (loading 1mol%). The solvent was dry and was degassed through freeze pump vacuum. The catalytic test afforded the attended carboxylated product. These experiments highlighted the importance of strictly controlling the reaction conditions, and in particular of having a degassed solvent for the carboxylation reaction. The solvent which performs better in these reactions has to be able to solubilize a good amount of CO_2 and It should be degassed before use. Starting from these trials, all carboxylations tests were carried on in degassed solvents.



Scheme 58. *Silver catalyzed carboxylation of 1-hexyne with $AgNO_3$ in DMSO.*



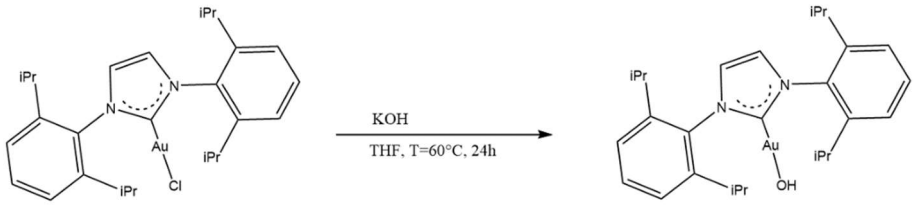
***Scheme 59**. Silver catalyzed carboxylation of 1-exyne in degassed DMSO. **A)** ^{1}H NMR Spectra of the silver catalyzed carboxylation on 1-hexyne in degassed DMSO. **B)**^{13}C NMR Spectra of the silver catalyzed carboxylation of 1-hexyne in degassed DMSO.*

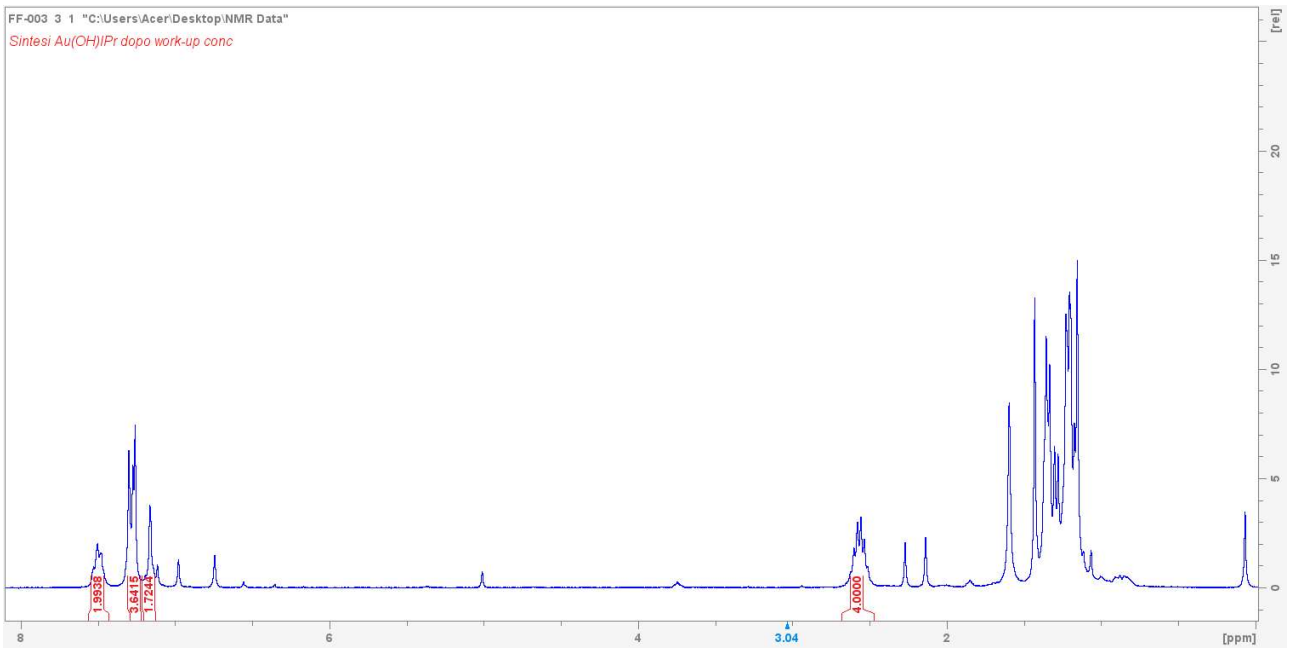
3.3 C-H Carboxylation with IPrAuOH

3.2.1 Synthesis of IPrAuOH

The gold catalyst which is used by Nolan and co-workers for the carboxylation of arenes is [1,3-Bis(2,6-diisopropylphenyl)-imidazol-2-ylidene] gold(I) hydroxide IPrAuOH. According to Nolan, this catalyst works well in the carboxylation of aromatics and heteroaromatics with sufficiently acidic C-H bonds [19]. We reasoned that a terminal alkyne should possess comparable acidity to the substrates employed by Nolan, hence it should be amenable to carboxylation under the same set of conditions. Thus, we set out to prepare Nolan's catalyst. Just for the first catalytic test the catalyst was synthetised from the hydroarylation catalyst IPrAuCl.

The synthesis consists in an exchange of anion, which was achieved upon mixing the complex with KOH at 60 °C for 24 hours in an inert atmosphere. The product was obtained with an isolated yield of 72% but the conversion was not complete since the signals of IPrAuCl are still present in the ^{1}H NMR spectra of the reaction crude (*scheme 60*).

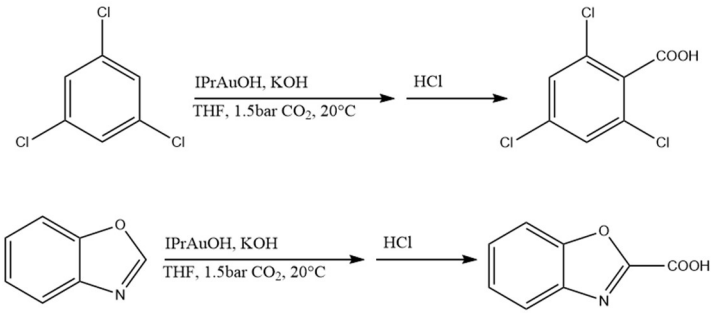




Scheme 60. *^{1}H NMR (300 MHz, $CDCl_3$) reaction crude of IPrAuOH after a filtration on celite.*

3.2.2 Carboxylation with IPrAuOH

Following the first aim of the thesis, several carboxylation tests were performed to reproduce the results of Nolan's group, but none of these tests afforded the attended result. Nolan's protocol for C-H carboxylation was first applied on 1,3,5 trichloro benzene and successively on benzoxazole without obtaining any trace of the carboxylated products.



Scheme 61. *Au catalyzed carboxylation of 1,3,5 trichloride benzene and benzoxazole.*

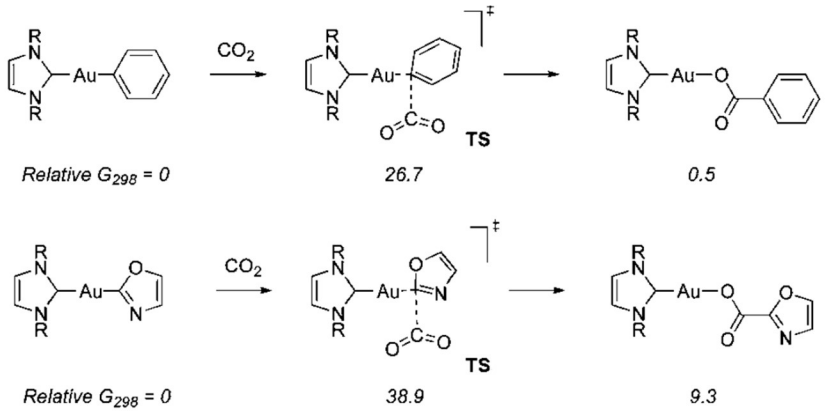
The first three tests were performed using 1,3,5 trichloro benzene as substrate and they were carried on using a pressurised reactor. In all these tests the attended product was never detected and there was the presence of another species in traces, which was firstly thought to be a product of stemming from a nucleophilic homocoupling condensation of the substrate. Subsequentially GC MS analysis did not confirm this hypothesis.

After these first failures another test with benzoxazole was carried on but the test did not provide any trace of the product. These inconclusive results induced us to think that there could have been a mistake in the methodology which was used. The only difference between the methods which was used for carrying out the test and Nolan's method was the absence of a pre solubilising phase of the CO_2 in the solvent. Since it was impossible to do it with the pressurised reactor which was used in the last tests, another trial was done using another suitable pressurised reactor (*scheme 61*). A last test was done in the new pressurised reactor using the benzoxazole as substrate. It was inserted under pressure and after a pre-solubilization phase but the experiment did not provide any trace of the carboxylated product as well.

Scheme 62. *Pressurized reactor used for the last catalytic carboxylation test of benzoxazole.*

All results suggest a lack of reactivity which leads us to suppose that the catalytic system is not effective. That is most likely because of the nature of the Au-C bonding, which seems to be not nucleophilic enough for the CO_2 insertion. To support this statement, there is an article of Ahlquist and Wendt which supports the lack of nucleophilicity of the C-Au bond towards CO_2 [66]. They proved that the CO_2 insertion is impossible to be achieved for a complex like that and that an eventual reaction of (NHC)Au(I)Ar complexes with strongly electrophilic substrates such as methyl triflate or methyl iodide to form toluene, biphenyl, and ethane were most likely to occur through an oxidative mechanism.

They calculated some thermodynamic parameters for the insertion of CO_2 in the Au-C bond of IMesAuPh. The free energy barrier is 26.7kcal mol^{-1}. Moreover, the reaction is calculated to be slightly endergonic with ΔG= 0.5 kcal mol^{-1}. Since the oxazolyl group is most likely less nucleophilic than a phenyl group, it is reasonable to expect that an Au (I)-oxazolyl complex is even less reactive toward CO_2 than IMesAuPh. Indeed, the barrier for CO_2 insertion is calculated to 38.9kcal mol^{-1}, indicating that the reaction should not be possible to observe unless a different mechanism is operating. However, they also calculate the reaction to be very endergonic, with ΔG =9.3 kcal mol^{-1}, which indicates that the reaction could never be observed, regardless of the mechanism.

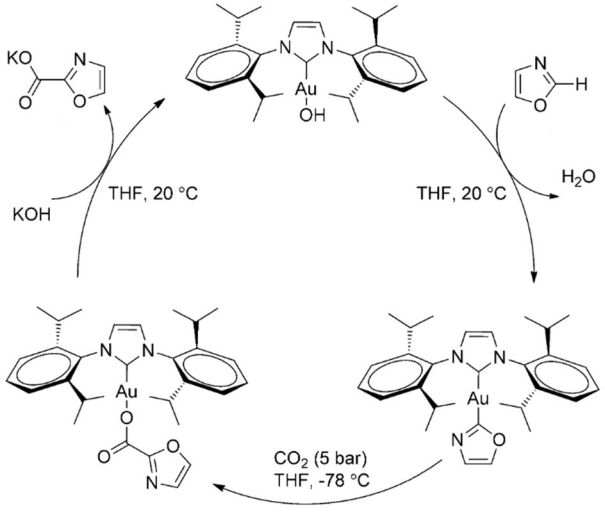


Scheme 63. *The free energy of activation in kcal mol^{-1} of reactions between the two NHC Au model complexes and CO_2.*

Recently, Nolan and co-workers further reported that decarboxylation of aromatic carboxylic acids occurred in the presence of the (IPr)Au–OH complex [67]. This reaction is simply the reverse reaction of CO_2 insertion and, since they provided calorimetric data, as well as different reactivities for a range of substrates, Ahlquist and Wendt decided to use this reaction as a test of the computational model. The measured reaction enthalpy for (IPr)Au–OH and 2,6-dimethoxybenzoic acid to give (IPr)Au-(2,6-dimethoxyphenyl), carbon dioxide and water was -9.4 kcal mol^{-1}. We calculated the corresponding reaction enthalpy (with the xylyl–NHC model ligand) to be -10.3 kcal mol^{-1}. The free energy barrier was calculated at 18.3 kcal mol^{-1}, which indicates that the reaction should be relatively rapid at room temperature. The corresponding reaction with benzoic acid as the substrate was calculated to have a barrier of 26.2 kcal mol^{-1} and should proceed much more slowly and, in the experiment, they do not observe any reaction of benzoic acid and very slow reaction of para-methoxy benzoic acid.

Furthermore, there are several aspects regarding the protocol which should be discussed. Firstly, Water which is a catalyst deactivator is supposed to be formed during the process and it is not so clear how the catalytic cycle can work in those conditions. In addition, Nolan's experimental setup of applying CO_2 pressure to the reaction mixture before addition of the substrate in the catalytic runs should result in the complete conversion of the KOH and IPrAuOH into the corresponding carbonates, which undoubtedly contradicts the proposed catalytic cycle. Actually, carboxylation of electron deficient heterocycles can also

be achieved using carbonates as a stoichiometric base under transition metal-free conditions [4] as reported in the chapter on base mediated carboxylations.

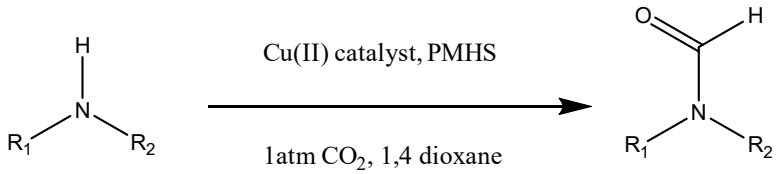


Scheme 64. *Proposed mechanism for Au-catalyzed C-H carboxylation.*

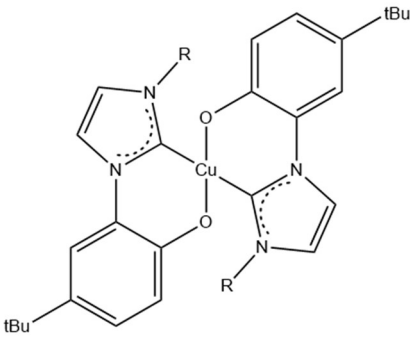
3.4 C-H Hydrocarboxylation with copper catalysts

3.4.1 Synthesys of phenolated NHC Cu(II) catalysts

There are several examples of C-H carboxylations carried out with Cu(I) in literature, but none with Cu(II) catalysts. Recently, the *Applied Organometallic Chemistry* group at DiSC has been studying and optimising a N-formylation protocol of amines which employs phenolated NHC Cu(II) catalysts (*scheme 49*) in combination with a silane such as the polymethylhydrosiloxane PMHS.

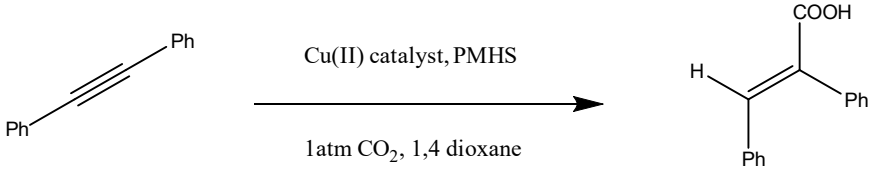


Scheme 65. *N-Formylation of amines with phenolated Cu(II) catalysts under 1 atm of carbon dioxide and with polymethylhydrosiloxane.*



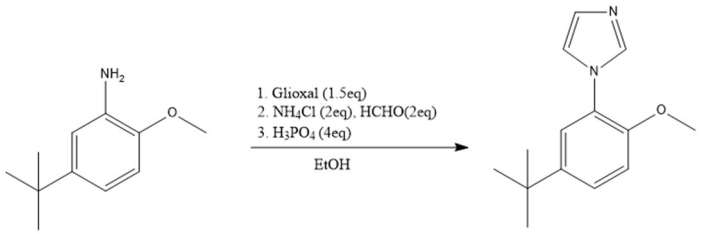
Scheme 66. *Generic structure of the phenolated NHC Cu(II) catalysts developed by the Applied Organometallic Chemistry group. The catalyst has been synthetized with different alkyl or aryl substituents R.*

The process has been subjected to some mechanistic studies and it is proved that an organosilane intermediate is generated during the process. Since a C-Si bond can be a valuable candidate to undergo a CO_2 insertion, it was hypothesized that the same Cu (II) catalyst could be used for promoting an hydrocarboxylation reaction of an alkyne similarly to the reported cases with Cu(I) catalysts. Hence, the Cu(II) catalyst was fully synthetised and tested for the carboxylation of diphenylacetylene.



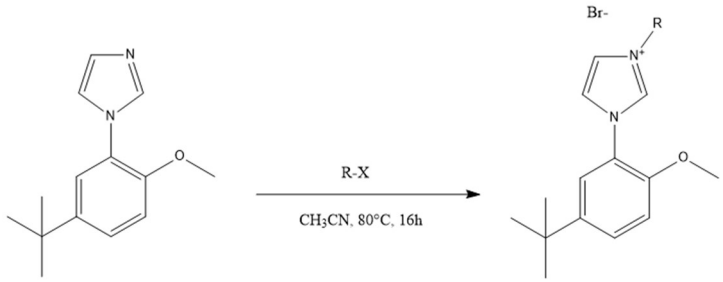
Scheme 67. *Hypothesized Hydrocarboxylation of diphenylacetylene with a phenolated Cu(II) catalyst under 1 atm of carbon dioxide and with polymethylhydrosiloxane.*

The initial precursor for the ligand was the 5-tert-butyl-2-methoxyaniline. The imidazolium ring was synthetised harnessing the Radziszewski reaction.



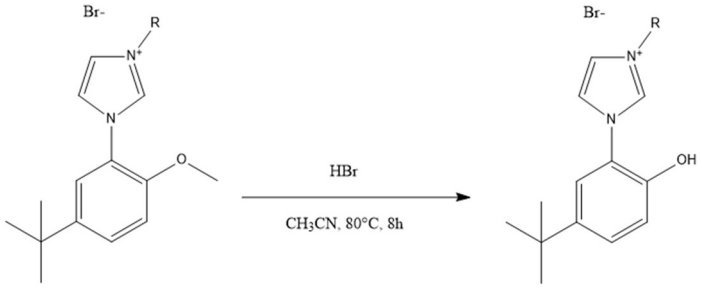
Scheme 68. *Synthesis of 4-t-butyl-2-(1H-imidazol-1-yl) anisole.*

The 4-t-butyl-2-(1H-imidazol-1-yl) anisole was functionalised with R=hexyl and benzyl. The substitution was achieved through reaction with the corresponding alkyl and aryl bromide in acetonitrile at 80°C.



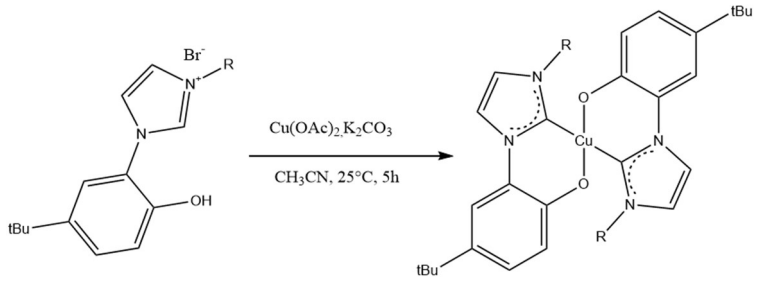
Scheme 69. *Functionalisation of the 4-t-butyl-2-(1H-imidazol-1-yl) anisole.*

The final synthetic step is the hydrolysis of the methyl group for obtaining the final ligand.



Scheme 70. *Hydrolysis of the methyl esther function to obtain the final ligand.*

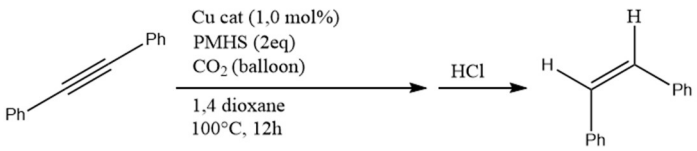
The synthesis of the complex is done in an inert atmosphere, by mixing the final functionalised ligand with potassium carbonate and copper acetate in acetonitrile at 25°C. The reaction is stereoselective since only the trans stereoisomer of the Cu(II) complex is obtained. The two complexes cannot be characterised using ^{1}H NMR spectroscopy since they are paramagnetic. Hence, they were characterised trough ESI-MS analysis, IR spectroscopy and elemental analysis. For the complex functionalised with R=Benzyl was possible to obtain crystals from the evaporation of ACN/Acetone solution and produce a crystallographic structure reported in *scheme 84*. For the complex functionalised with R=hexyl it was not possible to obtain a crystallographic structure.



Scheme 71. *Synthesis of the phenolated copper (II) catalyst.*

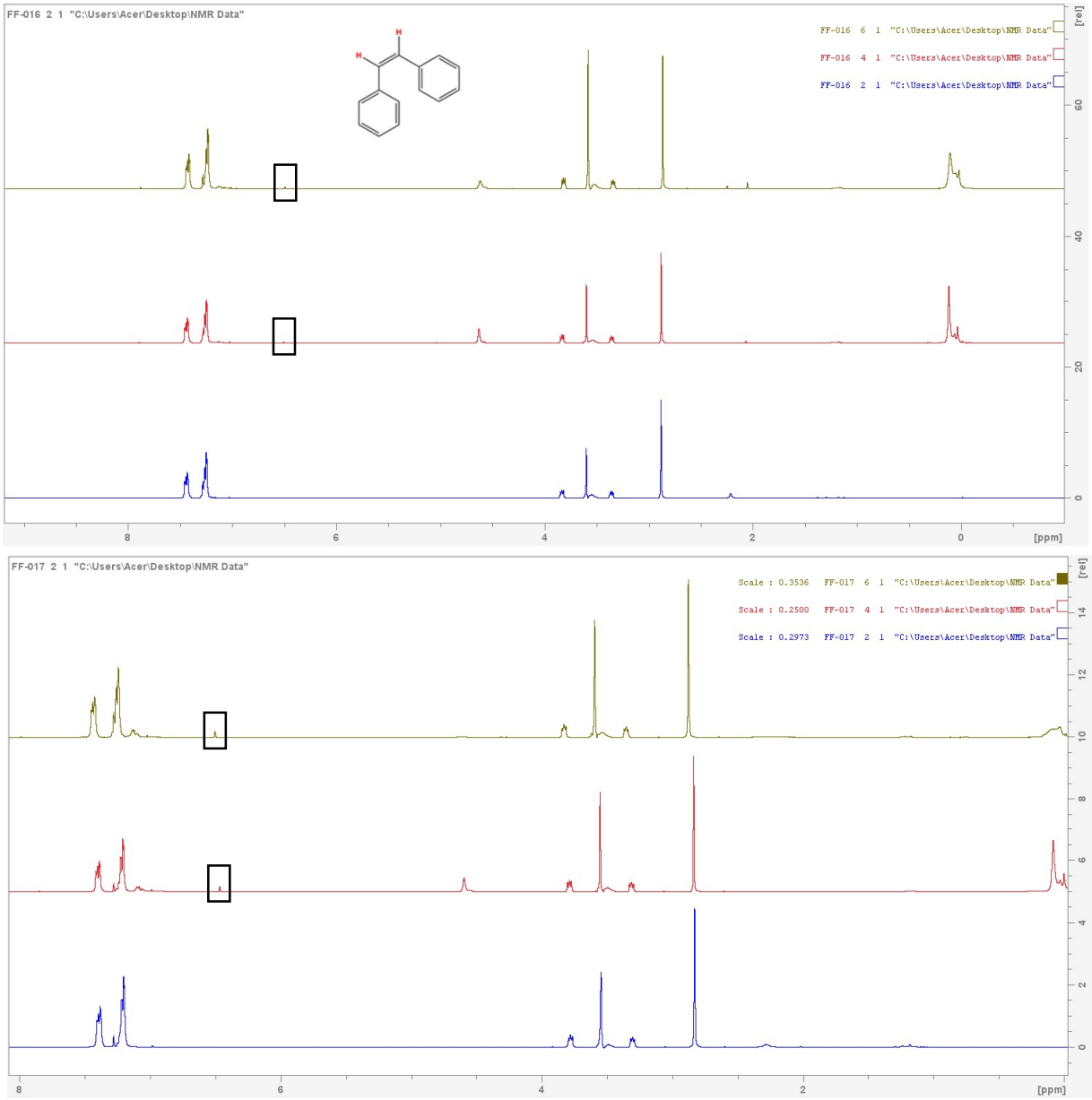
3.4.2 Hydrocarboxylation test on diphenylacetylene using the Cu (II) catalyst

The two catalysts functionalised with R=hexyl and benzyl were tested on diphenylacetylene using the same established methodology used for hydrocarboxylation with Cu(I) catalysts The tests took place in CO_2 atmosphere in 1,4 dioxane as solvent at 100°C with the addition of a silane.



Scheme72. *Catalytic test carried out with diphenylacetylene and using the copper (II) catalyst.*

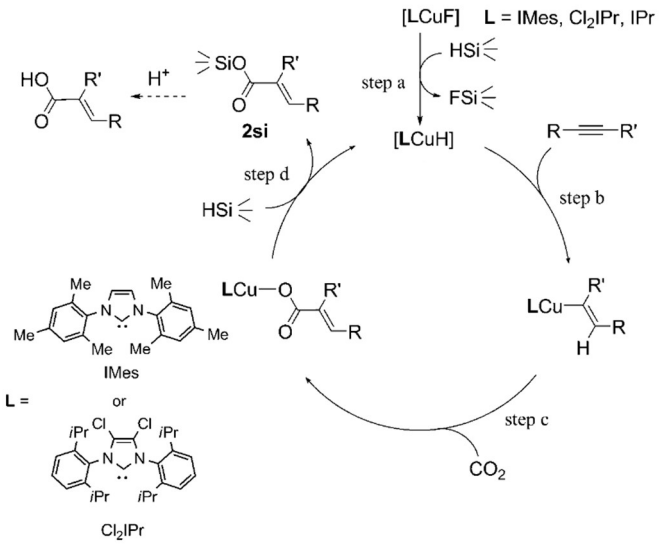
The silane acts as a hydride source, since in Cu(I) catalysed hydrocarboxylations is necessary to generate the copper hydride active species. It is important to highlight that for this Cu(II) catalyst is not known if the active species is a copper hydride as well. The silane which was chosen for the test was the polymethylhydrosiloxane PMHS, since the possibility of easy handling It and its cheapness. The reactions did not provide the expected hydrocarboxylation product, but traces of cis stilbene were detected. It is interesting to notice that also Cu(I) hydrocarboxylation processes reported in literature cited the presence of cis stilbene as a secondary product [25].



Scheme73. ***A)*** *^{1}H NMR (300 MHz, $CDCl_3$) of the reaction crude for test with the catalyst with R=benzyl at time 0h (blue line), at 2.5h (red line) and at 12h (green line).* ***B)*** *^{1}HNMR (300 MHz, $CDCl_3$) of the reaction crude for test with the catalyst with R=exyl at time 0h (blue line), at 2.5h (red line) and at 12h (green line). All the spectra were recorded saturating the signal of the solvent. The diagnostic signals of the cis stilbene are evidenced in red.*

3.5 C-H hydrocarboxylation with Copper (I) catalysts

The last part of the thesis work focused on C-H hydrocarboxylations with NHC copper (I) catalysts. The are some established carboxylation protocols which employs NHC copper (I) catalysts with silanes for the hydrocarboxylation of alkynes [25]. The mechanism with which the reaction takes place is quite known and it is composed of three main steps: the generation of a C-Cu species from the substrate, the insertion of CO_2 into the C-Cu bond to afford the copper carboxylate and the release of the copper with the regeneration of the catalyst.



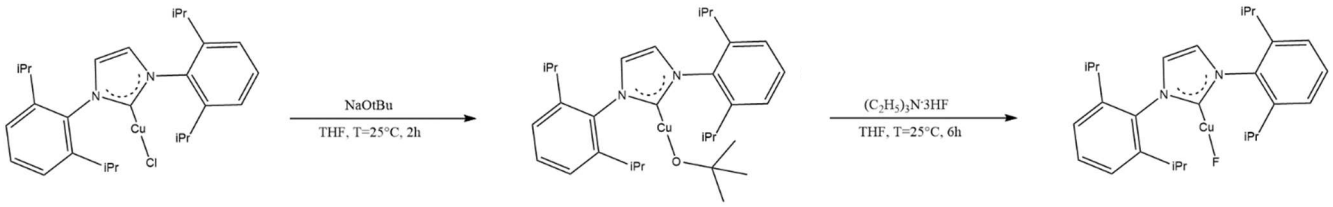
Scheme74. *Generic copper(I) hydrocarboxylation mechanism.*

Mechanistic studies revealed that the catalytically active species in these processes is a copper hydride which is generated by reaction of the catalyst with the silane. The efficiency of the NHC catalysts towards these processes depends on the NHC ligand and the counter anion. A less steric hindered ligand such as IMes proved to make the catalyst perform better than a more hindered one such as IPr. This behaviour is not easily rationalizable. Instead, the best counter anion is revealed to be the fluoride. A good explanation can be the high stability of the Si-F bond which make the formation of the active specie easier. For these reasons, IPrCuF and IMesCuF were synthetised with the aim to test them for hydrocarboxylation reactions.

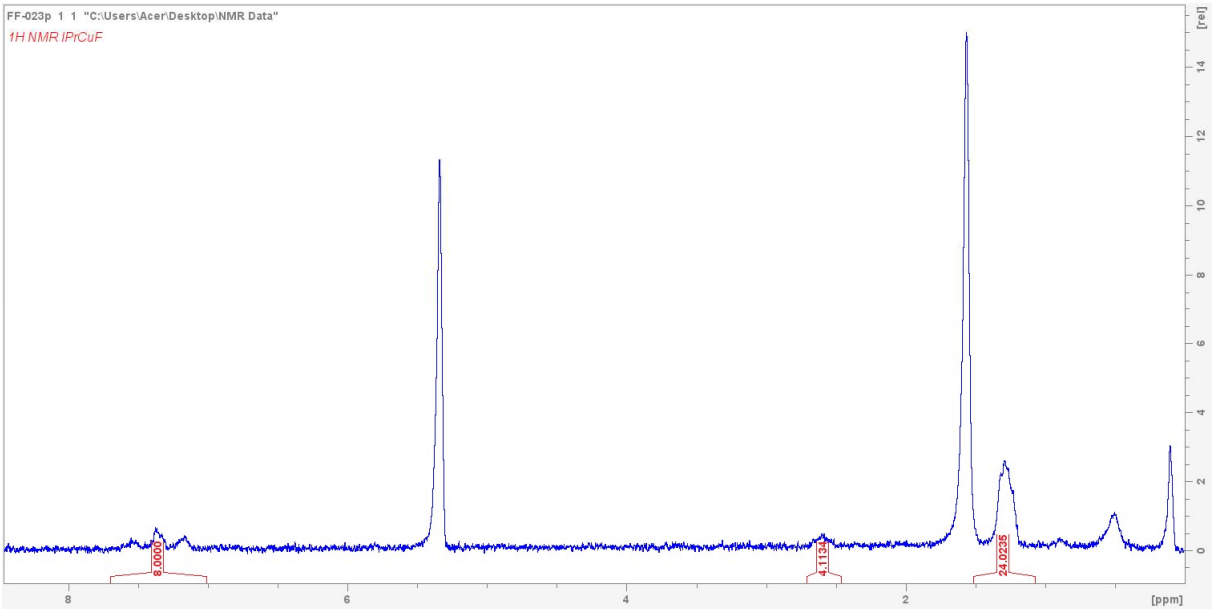
3.5.1 Synthesis of IPrCuF

IPrCuF was synthetised starting from the [1,3-Bis(2,6-diisopropylphenyl)-imidazol-2-ylidene] copper(I) chloride IPrCuCl through a double exchange of anion. All the synthetic steps were carried out in inert atmosphere and without light in order to avoid the decomposition of the copper complexes. The protocol which was followed was the one of Tsuji and co-workers.

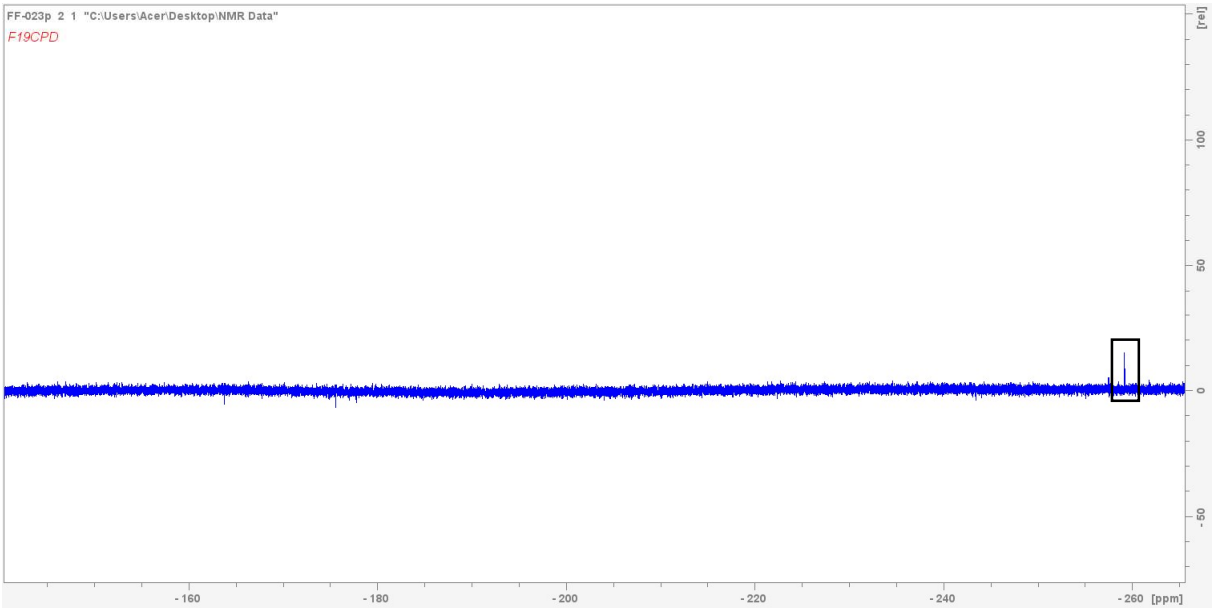
The first step was the exchange of the chloride ion with a tert-butoxide. The starting complex IPrCuCl was solubilized in dry and degassed THF and successively 1eq of sodium tert-butoxide was added. The final mixture was filtered by cannula and the fluorination step took place adding 0.3eq of $Et_3N{\cdot}3HF$. According to the ^1H NMR and ^{19}F NMR spectra the fluorinated complex IPrCuF was obtained with an isolated yield of 46%.



Scheme75. *Synthesis of IPrCuF starting from IPrCuCl.*



Scheme76. *^1H NMR (200 MHz, CD_2Cl_2) of IPrCuF*

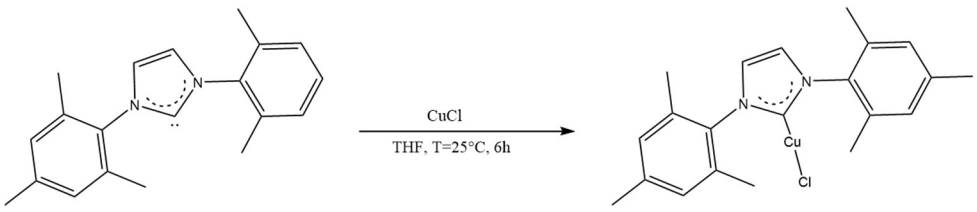


Scheme77. *^{19}F NMR (300 MHz, CD_2Cl_2) of IPrCuF. The diagnostic signal of the product is evidenced with a black square.*

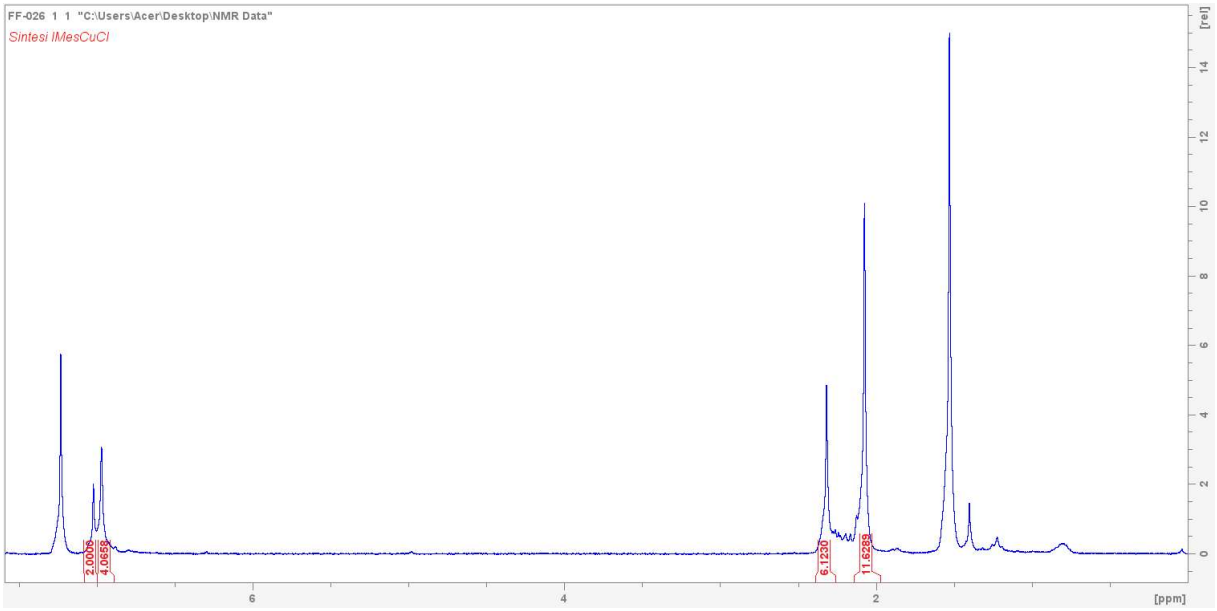
3.5.2 Synthesis of IMesCuF

The preparation of IMesCuF was much difficult than the synthesis of IPrCuF. Comparing the reported yields for the preparation of IPrCuF and IMesCuF, it can be observed that for the first is much higher than the second on [25].

The Tsuji and co-workers protocol employs IMes HCl but the first trial for the synthesis of IMesCuF was done starting from IMes as free carbene. Since, the free carbene is supposed to be the key intermediate in the synthesis, it was not expected to observe any relevant difference, except for the possible formation of the dimer. According to the ^{1}H NMR spectra of the reaction crude (*scheme 79*) IMesCuCl was detected while there were not any trace of dimer $(IMes)_2$. The product was obtained with an isolated yield of 52%.

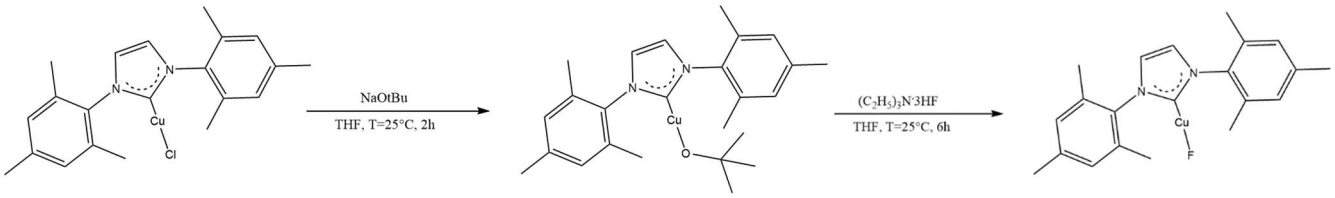


Scheme78. *Synthesis of IMesCuCl.*



Scheme79. *^{1}HNMR (300 MHz, $CDCl_3$) of the reaction crude for the synthesis of IMesCuCl.*

Successively, the reaction crude was filtered by cannula and like for IPrCuCl a double exchange of anion was attempted to be performed for obtaining the fluorinated complex. The fluorinated product was not detected since the lack of any signal in the ^{19}FNMR.



Scheme 80. *Synthetic route for the synthesis of IMesCuCl starting from IMesCuCl.*

After the first synthetic failure, other two trials were carried out starting from IMes HCl but without never obtaining the final product. The reason for these failures has to be imputed to practical issues. IMes is a less steric hindered ligand than IPr and this make its complexes more sensible to be handled, especially when they are in solution. In addition, the small scale of the synthesis made very difficult to perform the fluorination step, since the fluorination reactant has to be added in a very small amount, even if diluted.

At the end of thesis work just IPrCuF was synthetised and IMesCuF has to be still obtained and tested. The possible future aims for this study of copper catalysed hydrocarboxylations should focus on Cu(I) catalysts. In particular, it would be very interesting to focus on the ligand design to observe if it is possible to obtain a more performing catalyst for these copper (I) hydrocarboxylations.

4 Conclusion and Perspectives

The first goal of the thesis project revealed to be quite hard to be pursuited. It was possible to prove that the gold (I) catalysed hydroarylation is performable in a basic environment even if some specific conditions have to be respected. After this first discovery, C-H carboxylations were started to be studied with silver salts which proved to be able to catalyze these processes. Studying silver catalyzed carboxylations was also essential to understand the main issues regarding regarding that typology of reactions. Subsequently, a lot of time was spent studying gold (I) catalysed carboxylations for finding out that gold catalysts cannot be employed for C-H carboxylations due to the lack of nucleophilicity of the C-Au bond. On these bases, the initial idea of carrying out a C-H carboxylation coupled with an hydroarylation revealed to be possible in theory but not in practice, since the inefficiency of the hydroarylation process in a basic environment does not allow enough chances to develop a synthetic useful combined process. Hence, it was preferred to change the focus of the work on the perspective to deepen the knowledge regarding group 11 catalyzed carboxylations. The parallel work of the research group on a new Cu(II) catalyst made us think to develop an hydrocarboxylation process which employs Cu(II) instead that Cu(I), but the catalyst showed no catalytic activity towards hydrocarboxylations. The thesis ended with the synthesis of two NHC copper(I) catalysts with the idea of testing them in hydrocarboxylation processes.

5 EXPERIMENTAL SECTION

5.1 General Remarks

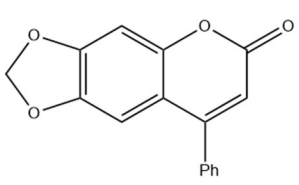
All manipulations have been carried out using standard Schlenk techniques under an atmosphere of argon. The reagents and solvents were purchased as high-purity products and used as received. ^{1}H, ^{13}C and ^{19}F NMR spectra were recorded on Bruker Avance 300 spectrometer at 298 K and ^{1}H and ^{13}C chemical shifts (δ) calibrated with respect to the signals of the deuterated solvent (^{13}C) and its protonated residue (^{1}H). The chemical shifts (δ) are reported in units of ppm and multiplicities of the peaks are expressed as s (singlet), br s (broad singlet), d (doublet), t (triplet), q (quartet), m (multiplet). Coupling constants are given in Hz. Analytical thin layer chromatography (TLC) was carried out on pre-coated aluminum sheets provided by Macherey-Nagel ALUGRAM Xtra SIL G/UV254. Components were visualized by treatments with aqueous $KMnO_4$ solution or by irradiation under UV light (254nm).

5.2 General procedures and characterization data

5.2.1 Au(I) catalyzed hydroarilation in presence of a base

The right quantity of [(IPr)AuOH] (0.012 mmol) and arene (2.5 mmol) were weighed and placed in a Schlenk-flask. Three cycles vacuum/argon were performed to ensure inert conditions. 0.75 ml of BMMIM NTf2, ethyl phenylpropiolate or phenylpropiolic acid (2.5 mmol) and $AgSbF_6$ (0.012 mmol) were added to the flask. The flask was placed in a thermostatic oil-bath at 50 °C. The process was monitored by ^{1}H NMR sampling with aliquots of the reaction crude at different times dissolved in 0.5 ml of $CDCl_3$.

8-Phenyl-6H-[1,3]dioxolo[4,5-g]chromen-6-one

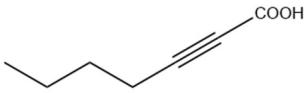


^{1}H NMR (300 MHz, CDCl3): δ 7.52-7.50 (m, 3H), 7.45-7.39 (m, 2H), 6.88 (s, 1H), 6.82 (s, 1H), 6.23 (s, 1H), 6.08 (s, 2H) ppm.

5.2.2 Carboxylation of 1-hexyne with silver salts

A dried Schlenk containing a stir bar was charged with the silver salt (0.02 mmol), Cs_2CO_3 (978 mg, 3.0 mmol), 1-hexyne (2.0 mmol) and 15 mL dry solvent were added with syringe respectively after purging the Schlenk with CO_2 three times. The Schlenk tube was filled with CO_2. The reaction mixture was stirred at 50°C for 12h, then the autoclave was cooled to room temperature and the remaining CO_2 was vented slowly. The reaction mixture was diluted with water (30mL) and extracted with hexane or CH_2Cl_2 (2 × 20 mL). The aqueous layer was acidified with aqueous HCl (6N, 20 mL) at low temperature and then extracted with diethyl ether (4 × 30 mL). The combined organic layers were washed with water and brine, dried over Na_2SO_4 and filtered. The solvent was removed under vacuum to afford the acid product.

2-Heptynoic acid

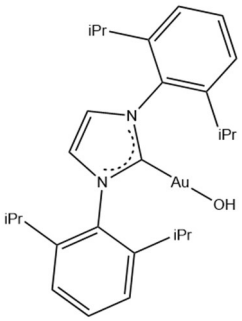


^{1}HNMR (300MHz, CDCl3): δ 2.34 (t, J= 7.5 Hz, 2H), 1.55 (p, J= 7.1 Hz, 2H), 1.42 (p, J= 7.3 Hz, 2H), 0.90 (t, J= 7.2 Hz, 3H).**^{13}C NMR (300 MHz, $CDCl_3$)** δ 154.24, 77.32, 31.53, 22.71, 19.51, 13.32.

5.2.3 Synthesis of IPrAuOH

A Schlenk tube was charged with [(IPr)AuCl] (40.0 mg, 0.0574 mmol) and KOH (3.22mg, 0.0574 mmol) in THF (0.8 mL). The reaction mixture was stirred for 24 hours at 20°C, then percolated through a short column of celite. The filtrate was concentrated under reduced pressure to give [(IPr)AuOH] as a white microcrystalline solid (28mg, 72% yield).

[Au(1,3-bis(2,6-diisopropylphenyl) imidazol-2-ylidene) (OH)]



^{1}H-NMR (300 MHz, $CDCl_3$): δ(ppm) 7.51 (m, 2H), 7.28 (m, 4H), 7.17 (s, J=2.4 Hz, 2H), 2.57 (m, 4H).

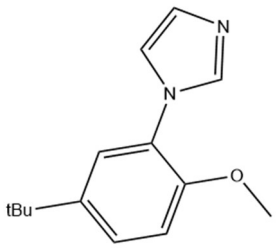
5.2.4 Carboxylation with IPrAuOH

A reaction tube was charged with a solution of [(IPr)AuOH] (9.0 mg, 0.015 mmol) and KOH (58.9 mg, 1.05 mmol) in THF (1.2 mL) under 1.5 bar pressure of CO_2. The mixture was incubated for 15 minutes at 20°C with vigorous stirring (1450 rpm). A solution of the aromatic substrate (1 mmol) in THF (0.3 mL) was introduced via CO_2-flushed syringe. The reaction was run at 20°C for 12 hours, then quenched with 1M aqueous HCl (2 mL). The product was taken up with EtOAc (3 × 3 mL) and the combined organic extracts were washed with 15% aqueous NaCl (4 mL), dried over Na_2SO_4 and concentrated under reduced pressure.

5.2.5 Synthesis of 4-t-butyl-2-(1H-imidazol-1-yl) anisole

A 250 mL, oven-dried, two-necked, round-bottomed flask is charged with 5-tertbutyl-o-anisidine (4.00 g, 22.3mmol), glyoxal (44.0mmol) and 100ml EtOH. The mixture was stirred for 1h and then formaldehyde (48.1mmol) and ammonium chloride (2.40 g, 44.6mmol) were added. The mixture was left on reflux at 94°C for 1h and then phosphoric acid was added. The mixture was left on reflux for 16h. The reaction crude was concentrated by vacuum and 40 ml of a KOH solution 40% was added. The organic phase was diluted with 15ml DCM, separated and concentrated under vacuum. The product was isolated by chromatographic column using AcOEt as eluent and characterised by ^{1}H NMR.

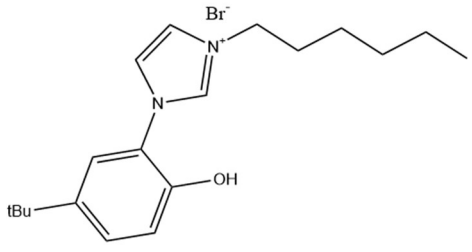
4-t-butyl-2-(1H-imidazol-1-yl) anisole



^{1}H-NMR (300 MHz, $CDCl_3$): δ(ppm) 7.77 (s, 1H), 7.37 (dd, J_1=8.6 Hz, J_2=2.4 Hz, 1H), 7.27 (d, J=2.4 Hz, 1H), 7.21 (1H), 7.17 (1H), 6.99 (d, J=8.6 Hz, 1H), 3.82 (s, 3H), 1.32 (s, 9H).

5.2.6 Synthesis of the ligand (R=hexyl) for the phenolated NHC copper(II)complex

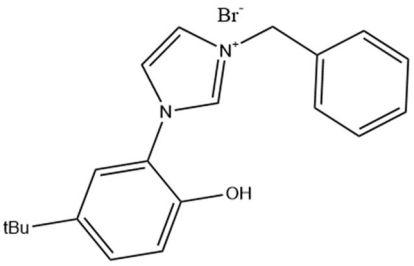
A Schlenk tube was charged with 4-t-butyl-2-(1H-imidazol-1-yl) anisole (500mg, 2.17mmol) and 3ml of ACN. 1-bromohexane (600 µL, 4.34mmol) was added and the reaction mixture was left for 16h at 80°C. 14ml of a solution 1:1 of HBr 40% and AcOH were added and the mixture was left stirred overnight. The reaction mixture was anhydrificated with Na_2SO_4, filtered and concentrated under vacuum to afford the product (780mg, 92%)



^{1}H-NMR (300 MHz, DMSO): δ(ppm) 9.56 (s, 1H), 8.03 (s, 1H), 7.65 (s, 1H), 7.63-7.57 (m, 2H), 7.28 (d, 1H), 4.25 (t, 2H), 1.87 (q, 2H), 1.30 (m, 16H) 0.87 (s, 3H).

5.2.7 Synthesis of the ligand (R=benzyl) for the phenolated NHC copper(II)complex

A Schlenk tube was charged with 4-t-butyl-2-(1H-imidazol-1-yl) anisole (1.00 g, 4.34mmol) and 6ml of ACN. benzyl bromide (1040 µL, 8.68mmol) was added and the reaction mixture was left for 16h at 80°C. 28 ml of a solution 1:1 of HBr 40% and AcOH were added and the mixture was left stirred overnight. The reaction mixture was anhydrificated with Na_2SO_4, filtered and concentrated under vacuum to afford the product (1,64mg, 95%).

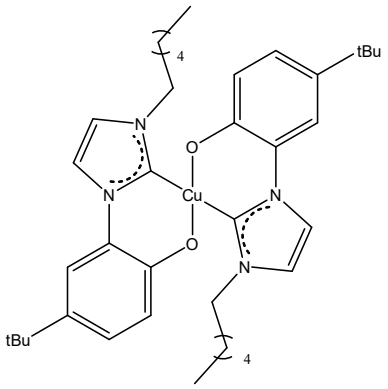


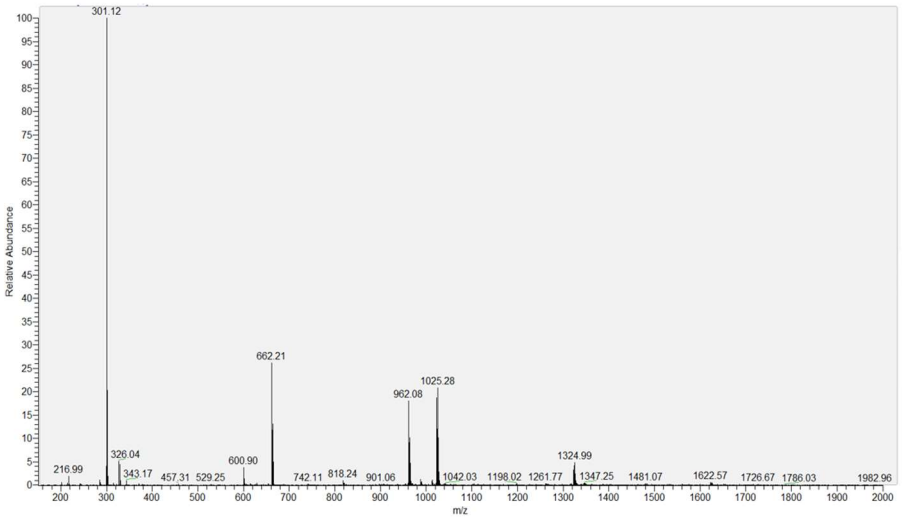
^{1}H-NMR (300 MHz, DMSO): δ(ppm) 9.79 (s, 1H), 8.04 (d, 2H), 7.63-7.26 (m, 8H), 5.53 (s, 2H), 1.30 (m, 9H).

5.2.8 Synthesis of phenolated NHC Cu(II) catalysts

The imidazolium salt (1mmol), K_2CO_3 (0,276g, 2mmol) and $Cu(OAc)_2$ (0,092g, 0,5mmol) were taken in a dry Schlenk flask and acetonitrile (20ml) was then added under inert atmosphere. The solution was stirred for 5h and a dark brown suspension was obtained. The suspension was removed under vacuum to obtain a solid residue. The residue was extracted with hexane and then the solution was filtered through a pad of celite through a closed frit to obtain a solution. Upon addition of toluene, a precipitate was obtained, which was collected by filtration and concentrated under vacuum obtaining the product. The phenolated-NHC Cu(II)-complex with R=hexyl was obtained with an isolated yield of 67%, while the complex with R=benzyl was obtained with an isolated yield of 27 %.

Characterisation data for the phenolated-NHC Cu(II)-complex with R=hexyl





Scheme 81 ESI-MS spectra of the *phenolated-NHC Cu(II)-complex with R=hexyl*. Interpreted signals: 301.12 $[H_2M^2]^+$, 662.21 $[Cu(M^2)_2 + H]^+$,962.08$[Cu(M^2)_3+2H]^+$,1025.28 $[Cu_2(M^2)_3]^+$,1324.99$[(Cu(M^2)_2)_2+H]^+$

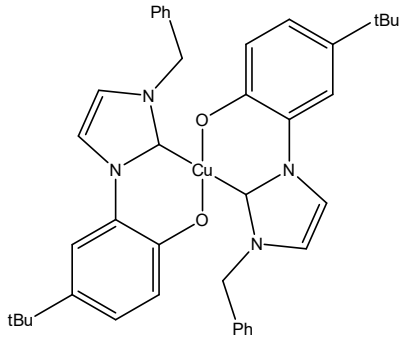
Elemental Analysis

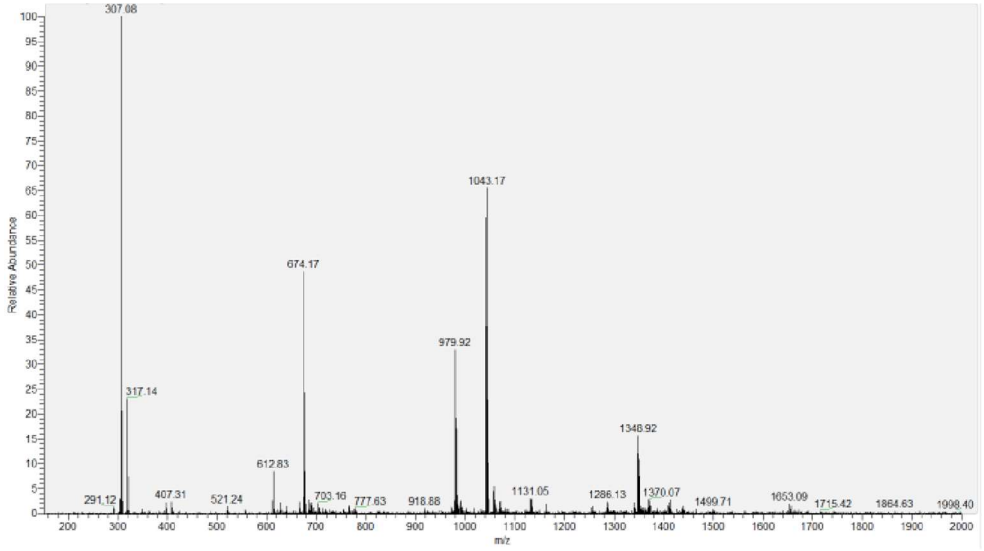
$C_{38}H_{54}CuN_4O_2$ 1.5 H_2O

Calculated percentages C/H/N 66.20/8.33/8.13

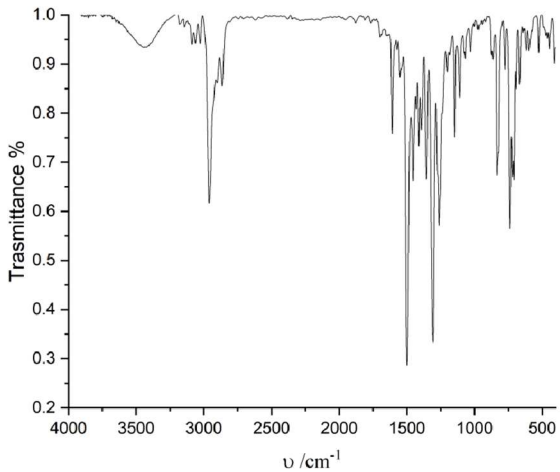
Analysis Result: C/H/N 66.19/8.42/8.05

Characterisation data for the phenolated-NHC Cu(II)-complex with R=benzyl





Scheme 82 ESI-MS spectra of the *phenolated-NHC Cu(II)-complex with R=benzyl.* Interpreted signals: *307.08 [H2L]+, 674.27 [CuL2 + H]+, 979.92 [CuL3 + 2H]+, 1043.17 [Cu2L3]+, 1348.92*



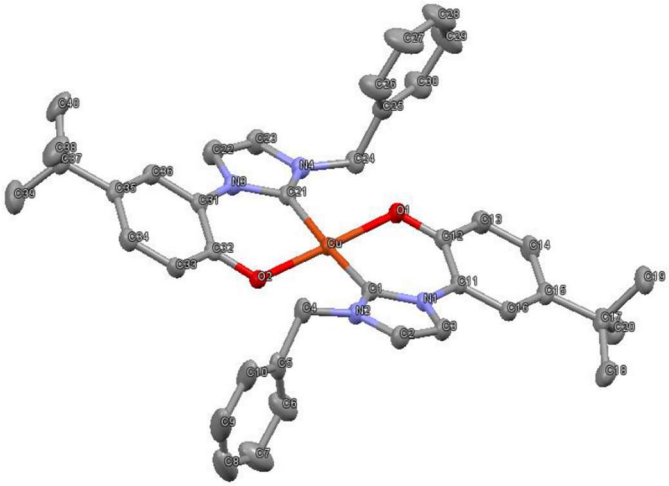
Scheme 83. *IR spectra of the phenolated-NHC Cu(II)-complex with R=benzyl. Signals: 1411.32, 1430.12, 1454.72, 1499.08, 1609.02, 2864.12, 2902.21, 2961.03.*

Elemental Analysis

$C_{40}H_{42}CuN_4O_2$

Calculated percentages C/H/N 71.25/6.28/8.31

Analysis Result: C/H/N 70.19/6.41/7.89

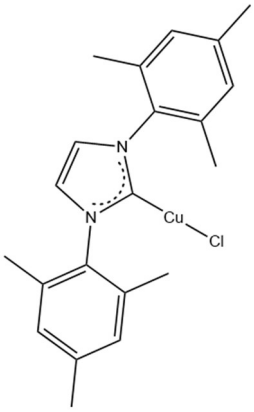


Scheme 84. *Crystallographic structure of the phenolated-NHC Cu(II)-complex with R=benzyl. The coordination geometry of the complex is square planar and the ligands are disposed in a TRANS configuration.*

5.2.9 Synthesis of IMesCuCl

A reaction tube was charged with the ligand IMesCl (152.2mg, 0.5mmol) and CuCl (55.4mg, 1mmol) in THF (5 mL). Successively, 0,5 mL of a solution 2M of KOtBu in THF was added. The mixture was stirred vigorously for 6h at 20°C. The reaction mixture was filtered on Celite and the filtrated was concentrated under vacuum affording the product (108,1mg, yield 54%).

Chloride [1,3-bis(2,4,6-trimethylphenyl) imidazol-2-ylidene]copper(I)



^{1}HNMR (300MHz, CDCl3): δ 7.06 (s, 2H), 6.98 (s, 4H), 2.36 (s,6H), 2.11 (s, 12H)ppm.

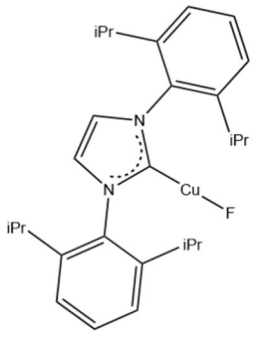
5.2.10 Synthesis of IMesCuOtbu and IPrCuOtBu

A reaction tube was charged with a Teflon-coated stirbar, with [IMesCuCl] or [IPrCuCl], anhydrous THF and potassium tert-butoxide (1eq). The resulting opaque brown solution was stirred for 2.0 h, filtered by cannula to be transferred in a round-bottomed flask in inert atmosphere used for the synthesis of the corresponding fluorinated complex.

5.2.11 Synthesis of IMesCuF and IPrCuF

To the round-bottomed flask containing [IMesCuOtBu] or [IPrCuOtBu] was added triethylamine tris(hydrofluoride) (0.33 eq) via a syringe. The resulting white suspension was stirred for 6 h and the solvent was removed on a vacuum line to afford the corresponding fluorinated complex. [IPrCuF] was obtained as white solid (80,2mg, yield 46%), [IMesCuF] was not obtained.

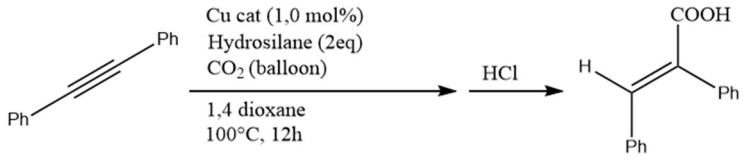
Fluoride[1,3-bis(2,6-di-i-propylphenyl) imidazol-2-ylidene] copper(I)



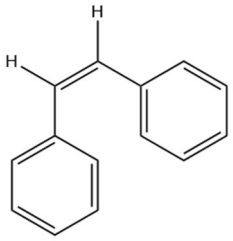
^{1}HNMR (300MHz, CD_2Cl_2): δ 7.54 (m, 2H), 7.37 (m, 4H), 2.63-2.49 (m, 4H), 1.30-1.23 (m, 24H)ppm. **^{19}FNMR (200MHz, CD_2Cl_2):** δ -259.23ppm.

5.2.12 Carboxylation with a Copper catalyst

A 20 mL schlenk tube dried with a heating-gun under vacuum was fitted with a balloon filled with CO_2, a rubber septum, and a teflon-coated magnetic stir bar. The schlenk tube was charged with diphenylacetylene (89.1 mg, 0.5 mmol) and the copper catalyst (0.01 mmol). The schlenk tube was evacuated and refilled with CO_2 three times. Then, the schlenk tube was covered with aluminium foil. Subsequently, dioxane (2.0 mL) and PMHS (1.0 mmol) was added via air-tight syringes, and the resulting mixture was stirred at room temperature for 1 min. Then the reaction tube was submerged in a pre-heated oil bath at 100 °C and the reaction was carried out for 12 h with stirring.



(Z)-1,2-diphenyl-ethene



HNMR (300MHz, CDCl3): δ 7,38-6,98 (m, 10H, aryl), 6,57 (s, 2H, alkyl) ppm

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