UNIVERSITAT ROVIRA I VIRGILI

# Pd-catalysed Carbonylations of Anilines in Ionic Liquids

**Nanette Zahrtmann**

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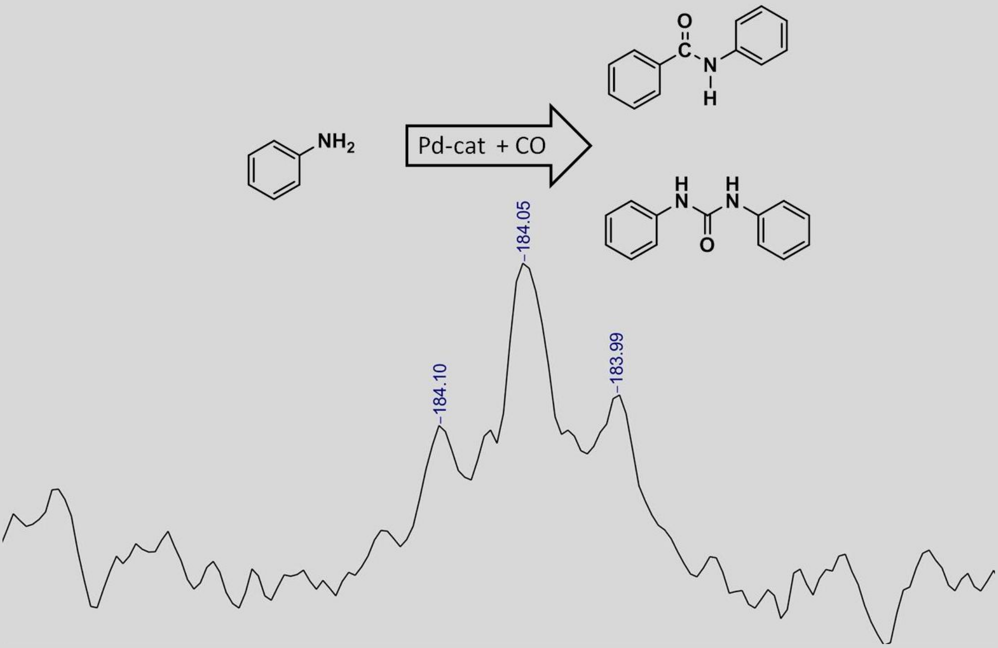

**DOCTORAL THESIS**
**2017**

Nanette Zahrtmann

# Pd-catalysed Carbonylations of Anilines in Ionic Liquids

## Doctoral Thesis

Supervised by

Cyril Godard,
Anders Riisager
&
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UNIVERSITAT ROVIRA i VIRGILI

Tarragona 2017

UNIVERSITAT ROVIRA I VIRGILI

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WE STATE that the present study entitled "Pd-catalysed Carbonylations of Anilines in Ionic Liquid", presented by Nanette Zahrtmann for the award of the degree of Doctor at Universitat Rovirar i Virgili, has been carried out under our supervision at the Department of Química Física i Inorgànica of Universitat Rovira i Virgili and at the Center for Catalysis and Sustainable Chemistry, Department of Chemistry of the Technical University of Denmark, and that it fulfills all the requirements to be eligible for the International Doctorate Award.

Tarragona, $3^{ed}$ of May 2017
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Many are stubborn in pursuit of the path they have chosen,
few in pursuit of the goal.
*Friedrich Nietzsche*

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# Abbreviations

| | |
|---|---|
| ATR-FTIR | Attenuated Total Reflection Fourier Transform Infra Red (spectroscopy) |
| BET | Brunauer-Emmet-Teller |
| BJH | Barret-Joyner-Halenda |
| BMIM | 1-butyl-3-methylimidazolium |
| BMMIM | 1-butyl-2,3-dimethylimidazolium |
| BPDHIM | 1-Butyl-3-propryl-4,5-dihydroimidazolium |
| BQ | 1,4-Benzoquinone |
| COD | 1,5-cyclooctadiene |
| DBU | 1,8-Diazabicyclo(5.4.0)undec-7-ene |
| DMSO | Dimethyl sulfoxide |
| DPPB | 1,3-Bis(diphenylphosphino)butane |
| DPPP | 1,3-Bis(diphenylphosphino)propane |
| DPU | Diphenyl urea |
| EMIM | 1-ethyl-3-methylimidazolium |
| EPS | Electron Spin Resonance (spectroscopy) |
| ESI-MS | Electrospray ionisation mass spectroscopy |
| FTIR | Fourier Transform Infra Red (spectroscopy) |
| GC-MS | Gas chromatography mass spectroscopy |
| HPLC | High pressure liquid chromatography |
| ICP-AES | Inductively coupled plasma atomic emission spectroscopy |

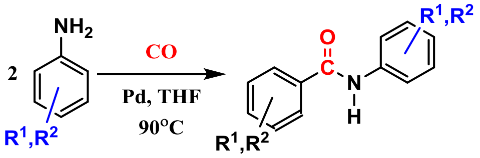
| | |
|---|---|
| IL | Ionic Liquid |
| IPr | 1,3-Bis-(2,6-diisopropylphenyl)imidazolylidene |
| LUMO | Lowest Unoccupied Molecular Orbital |
| MTBE | Methyl *tert*-butyl ether |
| NHC | N-heterocyclic carbene |
| NMR | Neutron Magnetic Resonance |
| NP | Nano particle |
| PEPPSI | Pyridine-Enhanced Precatalyst Preparation Stabilization and Initiation |
| PIL | Phosphonium Ionic Liquid |
| PPh | Triphenylphosphine |
| ppm | Parts per million |
| RTIL | Room Temperature Ionic Liquid |
| SILP | Supported Ionic Liquid Phase |
| TBP | *tert*-butyl phosphonium |
| TGA | Thermogravimetric Analysis |
| THF | Tetrahydrofuran |
| TOF | Turnover frequency |
| TON | Turnover number |
| XPS | X-ray photoelectron spectroscopy |
| XRF | X-ray fluorescence (spectroscopy) |

# Summary

This thesis describes the study of several palladium catalysts with commercially available phosphorus and nitrogen donor ligands, either as sole ligand or in combination with N-heterocyclic carbenes. The palladium systems were applied in the carbonylation of anilines for the formation of amides and ureas. The thesis is divided into four chapters. The first chapter is a brief introduction to the carbonylation chemistry of homogeneous palladium catalysts. Carbonylation reactions involving ionic liquids and SILP catalysts are also discussed. The second chapter deals with the formation of amides from anilines. A novel catalytic system is disclosed and a mechanism is proposed. The third chapter covers work on two catalytic systems for the formation of diphenyl urea involving ionic liquids as solvent and reaction facilitator. The fourth chapter describes the transfer of the ionic liquid mediated oxidative carbonylation of aniline into continuous flow conditions. SILP technology was applied for the heterogenization of the molecular catalyst.

## Preparation of Benzamide by Carbonylation of Anilines

In this chapter, a previously unpublished palladium based catalytic system for the highly selective transformation of anilines into benzamides is described. The reaction proceeded smoothly without the need for prior activation of the aniline.

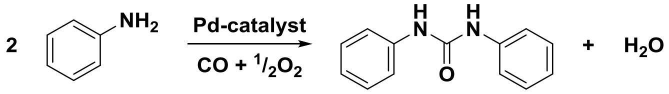


Formation of benzamides from anilines and CO.

Notably, the catalytic system is additive free, robust and utilizes commercially available ligands. A wide range of primary anilines including sterically hindered substrates were efficiently converted into benzamides in high yield. For this transformation, three catalytic cycles involving the cleavage of primary arylamine C-N bond is proposed. To the best of our knowledge, this is the first catalytic example of this reaction, without prior activation of the aniline.

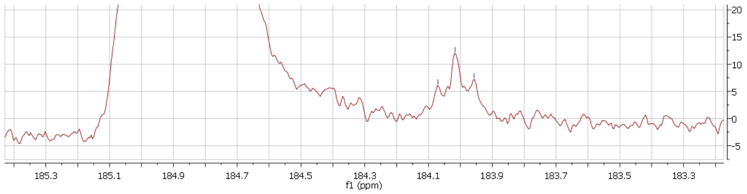
## Palladium Catalysed Carbonylation of Aniline in Ionic Liquids

This chapter deals with the oxidative carbonylation of aniline in a biphasic ionic liquid/toluene system. In this reaction, the presence of ionic liquid was crucial for the outcome of the reaction. Furthermore, the nature and the amount of ionic liquid strongly influenced the catalyst activity. Two hypotheses, with respect to the cause of this influence, were tested and the results are discussed. An *in-situ* high-pressure NMR experiment was performed to shed light on the mechanism of the reaction and supports previously reported proposals. A proposed intermediate was confirmed and information on the formation of this intermediate was obtained.



Synthesis of substituted urea from aniline.

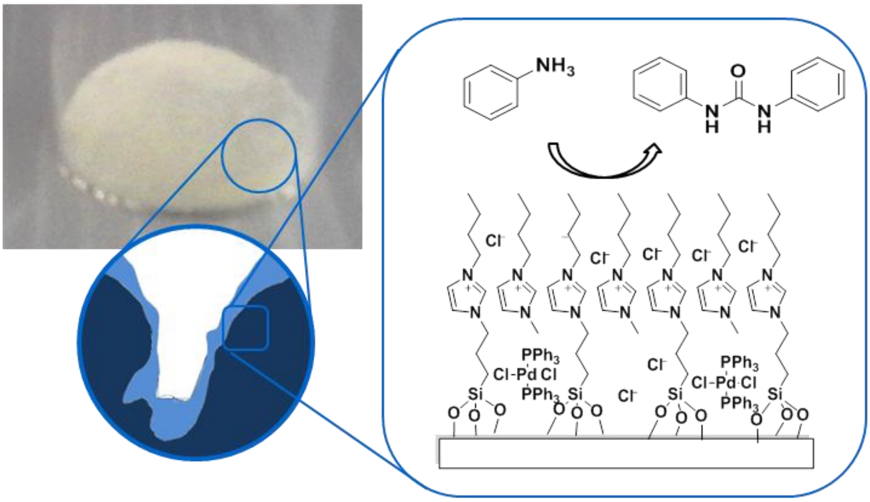
Selective oxidative carbonylation of aniline to diphenylurea was carried out in the presence of a catalytic system comprising of [$PdCl_2(PPh_3)_2$] and [BMIM][Cl] with a TOF of 15600 $h^{-1}$ and 1900 $h^{-1}$ when benzoquinone or $O_2$ were used as oxidants, respectively. The TOF achieved with benzoquinone as oxidant was, to the best of our knowledge, the highest reported so far under mild reaction conditions (140ºC and 10 bar). In order to investigate the influence of the ionic liquids, several cations and anions were applied. The best results were achieved with [BMIM][Br] while the employment of [BMIM][($(CF_3SO_2)_2$] drove the product to spontaneously separate. Recycling experiments were conducted but loss of activity was observed after the first reuse. Decomposition of the catalyst was observed during workup but leaching of catalyst into the toluene phase cannot be excluded as a cause for the unsuccessful recyclability.



*In-situ* NMR of the carbonylation reaction.

## Oxidative Carbonylation of Aniline in Continuous Flow conditions

The oxidative carbonylation of aniline was performed under bach and continuous flow conditions applying CO and air as the gaseous reactants with a Pd-SILP catalyst. The SILP catalyst was prepared from alkyl-imidazolium functionalized silica in order to enhance the adhesion of the imidazolium ionic liquid to the solid support.



The SILP principle applied in this project.

Silicas bearing two different attached imidazoliums were prepared, characterized and applied as supports. Their characterization indicated, that functionalisation mainly took place inside the silica pores. Under batch conditions, good activity and recyclability were obtained with SILP, while support only impregnated with the homogenous catalyst was not active. Continuous flow experiments were performed with the prepared SILP materials. Steady-state conditions were not obtained due to the rapid deactivation of the catalyst under continuous flow. The characterization of the catalyst material after reaction indicated that leaching of both palladium and non-anchored IL during the reaction could be the cause of the catalyst deactivation. Leaching of the catalytically active components of the SILP material was most likely caused by the large amounts of solvent passed over the catalyst. The partial miscibility of solvent and ionic liquid caused the removal of the ionic liquid layer, containing the active catalyst from the solid support, and thus deactivated the catalyst. In this regard, the imidazolium functionalisation of the silica surface did not provide the anticipated anchoring of the non-covalently bound IL as leaching was observed regardless of the support material applied for the preparation of the SILP.

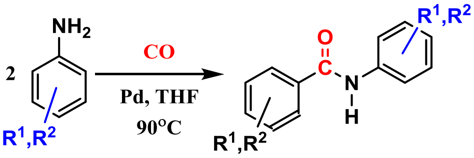
Pd-catalysed Carbonylations of Anilines in Ionic Liquids
Nanette Zahrtmann

# Resum

Aquesta tesi descriu l'estudi de diversos catalitzadors de pal·ladi amb lligands donadors de fòsfor i nitrogen, ja sigui com a lligand únic o en combinació amb carbens N-heterocíclics. Els sistemes catalítics de pal·ladi s'han aplicat en reaccions de carbonilació d'anilines com a substrat per a la formació d'amides i urees. La tesi es divideix en quatre capítols. El primer capítol és una breu introducció a la química de reaccions de carbonilació catalitzades per complexos de pal·ladi en sistemes homogenis o sistemes heterogeneïtzats. Es presta especial atenció a les reaccions de carbonilació que impliquen líquids iònics (LI) i catalitzadors suportats en líquids iònics, "Suppored Ionic Liquid Phase" (SILP). El segon capítol tracta la formació d'amides a partir d'anilines. Es descriu un nou sistema catalític i es proposa un mecanisme de reacció. El tercer capítol fa referència al treball realitzat amb dos sistemes catalítics per a la formació de difenil urea, en el que es mostra que la utilització de líquids iònics com a dissolvent millora els resultats de la reacció. El quart capítol s'ocupa de la heterogeneïtzació dels líquids iònics suportant-los en sílice i ser utilitzats com a catalitzadors en la reacció de carbonilació de l'anilina en sistemes de flux continu.

## Preparació de Benzamida mitjançant la carbonilació d'anilines

En aquest capítol es descriu un sistema catalític de pal·ladi, no publicat prèviament, per a la transformació d'anilines en benzamides. La reacció va procedir amb alta selectivitat, sense additius i sense la necessitat d'activació prèvia de l'anilina.

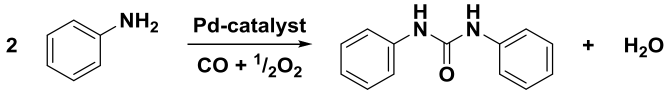


Formation of benzamides from anilines and CO.

Cal destacar que el sistema catalític no requereix additius, és robust i utilitza lligands disponibles comercialment. Una àmplia gamma d'anilines primàries incloent substrats estèricament impedits van ser convertits de manera eficient en benzamides amb alt rendiment. Per a aquesta transformació, es proposa un cicle catalític que implica l'escissió de l'enllaç C-N de arilamina primària. Pel que sabem aquest és el primer exemple catalític d'aquesta reacció, sense l'activació prèvia de l'anilina.

## Carbonilació d'anilina catalitzada per pal·ladi en líquids iònics

Aquest capítol tracta de la carbonilació oxidativa d'anilina en un sistema bifàsic toluè /líquid iònic. En aquesta reacció, la presència de líquid iònic va ser crucial per al resultat de la reacció. A més, la natura i la quantitat de líquid iònic van influenciar fortament l'activitat del catalitzador. Es van plantejar i discutir dues hipòtesis, pel que fa a la causa d'aquesta influència.Es va realitzar un experiment in-situ de RMN d'alta pressió per esbrinar el mecanisme de la reacció i donar suport a les propostes anteriorment publicades. Es va identificar un intermedi que suporta la proposta de mecanisme.



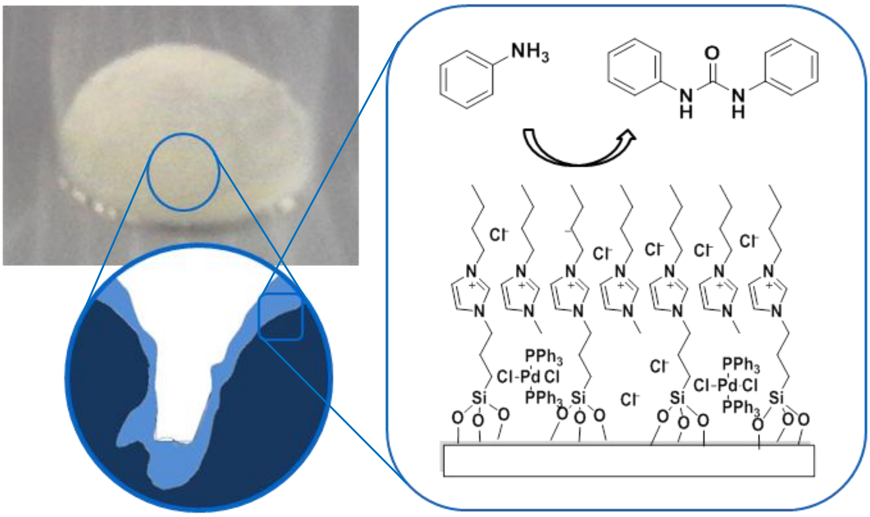
Síntesi de difenil urea a partir d’anilina en presència d'oxigen.

La carbonilació oxidativa d’anilina per l’obtenció de difenil urea es va realitzar en presència d'un sistema catalític que comprèn [$PdCl_2(PPh_3)_2$] i [BMIM][Cl] amb un TOF de 15600 $h^{-1}$ i 1900 $h^{-1}$ quan benzoquinona o $O_2$ van ser utilitzats com oxidants, respectivament. El TOF obtingut amb benzoquinona com a oxidant és, el més alt publicat fins ara en condicions suaus de reacció ($140^{o}$C i 10 bar). Per tal d'investigar la influència dels líquids iònics, es van emprar diversos cations i anions. Els millors resultats es van aconseguir amb [BMIM][Br], mentre que utilitzant [BMIM][$Tf_2N$] va donar lloc a la separació espontània del producte. Es van dur a terme experiments de reciclatge però es va observar pèrdua d'activitat després de la primera reutilització. Es va observar descomposició del catalitzador durant el tractament si bé no espot excloure la lixiviació del catalitzador en la fase del toluè com una causa per la manca de reciclabilitat.

*In-situ* RMN de la reacció de carbonilació oxidativa d'anilina.

## Carbonilació oxidant d'anilina en condicions de flux continu

La carbonilació oxidant d'anilina es va realitzar en condicions batch i en condicions de flux continu aplicant CO i aire com a reactius gasosos amb un catalitzador de Pd-SILP. El catalitzador SILP es va preparar a partir de sílice funcionalitzat amb alquil-imidazol per a millorar l'adhesió del líquid iònic d’imidazol al suport sòlid.



Principi de SILP aplicat en aquest projecte.

Es van preparar sílices funcionalitzades amb dues salts d'imidazol diferents, van ser caracteritzades i aplicades com a suports. La seva caracterització va indicar, que la funcionalització va tenir lloc principalment dins dels porus de la sílice. En conditions batch, bona activitat i reciclabilitat es van obtenir amb els SILP, mentre que el suport únicament impregnat amb el catalitzador homogeni no va ser actiu. Experiments de flux continu van ser realitzats amb els materials SILP preparats. No es van poder aconseguir condicions steady state no es van obtenir a causa de la ràpida desactivació del catalitzador sota flux continu. La caracterització del catalitzador després de la reacció va indicar que la lixiviació tant del pal·ladi com del LI no suportat durant la reacció podria ser la causa de la desactivació del catalitzador. La lixiviació dels components catalíticament actius del material SILP va ser molt probablement causada per les grans quantitats de dissolvent que es van fer passar sobre el catalitzador. La miscibilitat parcial del dissolvent i del líquid iònic va causar l'eliminació de la capa de líquid iònic que contenia el catalitzador actiu del suport sòlid, i per tant va desactivar el catalitzador. En aquest sentit, la funcionalització de la sal d'imidazol de la superfície de la sílice no va proporcionar l'esperat ancoratge del LI no covalentment unit ja que es va observar lixiviació independentment del suport utilitzat per a la preparació dels SILP.

# Chapter 1

# Introduction

# Introduction

## 1.1 Catalysis

The first descriptions of catalytic processes appeared in the scientific literature in the 18'th century[1] and in 1835, Berzelius coined the terms catalyst and catalysis to describe the observations of compounds that were reacting but not consumed.[2] In 1909, Oswald received the Nobel Prize in chemistry for his work on catalysis, chemical equilibria and reaction velocities[1] and the present day definition "A catalyst is a substance which increases the rate at which a chemical reaction approaches equilibrium without becoming itself permanently involved" is an adaptation of Oswald's 1895 statement.[3] When a catalyst increases the rate of a reaction, the catalyst provides a new reaction pathway with a lower activation energy.[4] To illustrate this, an energy diagram of the bimolecular transformation of A and B to C and D is shown in Figure 1. The uncatalysed reaction is exemplified by the top trace. In this case the reaction goes through a highly energetic intermediate AB. A catalyst provides an alternative reaction mechanism with different transition states, which are lower in energy, either by voluntary formation of an activated species (i) or through an initial activation step (ii).

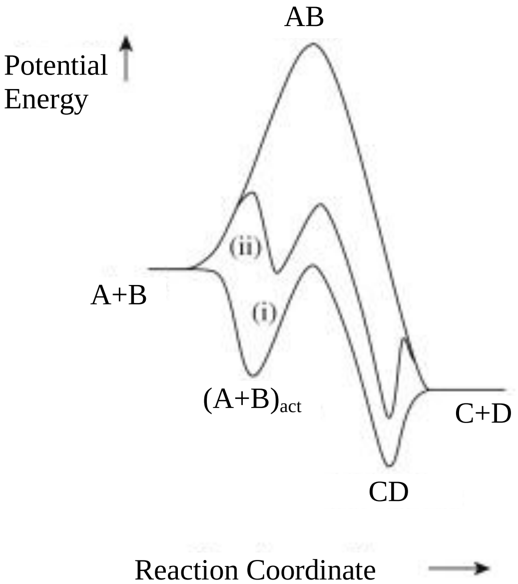


**Figure 1.** Schematic potential-energy diagram for the course of a generic bemolecular reaction between A and B to B form C and D.[5]

It is the lower activation energy that enables reactions which do not occur in the absence of a catalyst or require forcing reaction conditions, making the catalytic effect purely kinetic. The catalyst provides an alternative mechanism with different transition states while the overall free energy of a reaction remains the same.

To describe the reactivity of a catalyst, a few terms are used that do not apply to other fields of chemistry. These are the turnover number (TON), that quantify the catalyst activity for the duration of the reaction and turnover frequency (TOF) which is a measure of the catalyst activity per time unit. By considering both TON and TOF, information on the catalyst life-time and catalyst peak performance are thus obtained. There is a general consensus that TON is calculated as mole of substrate converted per active catalyst site but especially in the case of heterogeneous catalysts, the number of active sites is difficult to quantify. TOF is calculated as TON per time unit and should show the maximum performance of the catalyst. Therefore, the TOF should be calculated for a conversion below 20% and reflects the initial rate of reaction. Both TON and TOF are very useful for quantifying and understanding the performance of a catalyst when the conditions under which they have been measured are taken into account.

In general, catalysts may be classified as either homogeneous or heterogeneous depending on, whether the catalyst belongs to the same phase as the reactants. The anchoring of a homogeneous catalyst onto an insoluble support gives rise to a third category usually described heterogenized catalysts. These 3 types of catalysts will be briefly depicted in the following sections.

### 1.1.1 Heterogeneous Catalysis

In chemistry, heterogeneous catalysis refers reactions where catalyst and reactants reside in separate phases. The great majority of heterogeneous catalysts are solids and applied in gas or vapour phase reactions, which imply surface reactions. In many instances, the catalytic surface is a metal nanoparticle or an oxide surface as in the case of zeolite catalysts. The rate of diffusion of substrate both in the boundary layer and in the catalyst pores, adsorption of substrate and desorption of product are important factors governing catalyst acctivity.[6,7] The presence and accessibility of catalytically active sites is of course essential for the activity and is often closely linked to the surface area of the catalyst material. The formation of active sites on a heterogeneous catalyst relies on the reduced number of neighbours that a surface atom has in the crystal lattice. The shortage of neighbours leads to coordination vacancies that can be occupied by the substrate.

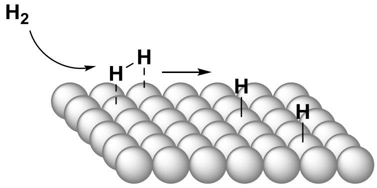


**Figure 2.** Surface $H_2$ adsorption and dissociation.

The first example of documented heterogeneous transition metal catalysis is the Contact Process where sulfur dioxide is oxidized to sulfur trioxide by air, for the production of sulfuric acid. When the process was first employed for industrial production in 1880, pumice supported platinum was used as catalyst. This material was replaced by a supported vanadium catalyst after 1900.[8] In 2000, 167 million tons of $H_2SO_4$ was produced by the vanadium pentoxide/pyrosulfate catalyzed contact process. However, the catalyst is no longer considered solid as the salt mixture on the catalyst melts under process condition.[9]

Heterogeneous catalysts are preferred in bulk chemical production due to the established continuous processes that enable large scale production, the easy handling of stable solids and easy product separation.[4] Industrially relevant catalyst are also thermally stable as the industrial processes often take place at harsh conditions (Contact process: 400-450°C; Haber-Bosh process: 20 MPa, >400°C).[9,10] Furthermore, heterogeneous catalysts are often applied to gas or vapour phase reactions in order to avoid the sintering of the NPs. The harsh conditions under which heterogeneous catalysts are active are also mentioned as one of the major disadvantages of heterogeneous catalysis as the high temperatures can promote side reactions.[11] Another challenge concerning heterogeneous catalysis is the difficulty of knowing the reaction mechanism.[6]

**Table 1.** Advantages and disadvantages of heterogeneous catalysis.

| Properties of Heterogeneous Catalysis | Advantage | Disadvantage |
|---|---|---|
| Chemical technology | √ | |
| Handling | √ | |
| Product separation | √ | |
| Thermal stability | √ | √ |
| Activity | √ | √ |
| Selectivity | | √ |
| Mechanistic knowledge | | √ |

Understanding the reaction mechanisms of heterogeneous catalysts and the nature of the catalytically active species is a laborious effort and has long been hampered by the lack of mature technologies for the direct study of the catalytic active surfaces.[6,12] In summary the advantages and disadvantages, that led researchers to test thousands of catalysts, are listed in Table 1.

Several bulk processes have been put on steam before the reaction mechanism was known as in the case with the Haber-Bosch process.[12] A better understanding of the surface chemistry of metals and oxides,[13,14] coordination chemistry at surfaces and kinetics assisted by computational methods have enabled a more systematic search for active catalysts.[12] Scanning electron microscopy and tunnelling electron microscopy under moderate gas pressure have both provided access to observation of absorbed reactants on solid catalyst surfaces and hence important information for the understanding of solid and supported NP catalysis.[6] The same can be said of Raman spectroscopy and attenuated total reflection infra red spectroscopy (ATR-FTIR) under *in-situ* conditions, which are new but promising techniques for the study of surface reactions.[15]

### 1.1.2 Homogeneous Catalysis

As opposed to heterogeneous catalysts, homogeneous catalysts are contained in the same phase as the reagents. An early example of homogeneous catalysis is the predecessor of the contact process: The lead-chamber process for the production of sulfuric acid. In this process, sulfur was oxidized to $SO_3$ by $NO_2$. NO was then re-oxidized by air allowing the reaction to proceed through a $N^{+4}/N^{+2}$ catalytic cycle.[3] The lead-chamber process is, in contrast with the contact process, a homogeneous reaction because both reactants and catalyst are in the gaseous phase. Nitrogen might be considered an unusual catalyst but other examples of non-metal catalysts involve boron, carbon, silicium, phosphorus, sulfur and selenium based catalysts, which are also gaining momentum as earth abundant catalysts.[4,16] A more familiar example of metal-free homogenous catalysis is acid-catalysis such as esterification, acetylation and aldol reactions.[17,18] However, homogeneous catalysis is most frequently discussed in the context of transition-metal catalysts and strong ties exist between organometallic chemistry and homogeneous catalysis. Organometallic catalysts consist of transition-metal atom(s) surrounded by organic and/or inorganic ligands allowing every metal atom to act as an active site. The formation of such complexes is enabled by the d-orbitals of the metal through different bonding modes depending on the nature of both the metal and the ligand.[19] Even small changes in the ligand environment can have large effects on the catalysts activity and selectivity. This makes the understanding of the interaction between metal and ligands a key parameter for the stabilisation and tuning of the catalyst. Both electronic and steric influence have to be considered.[20]

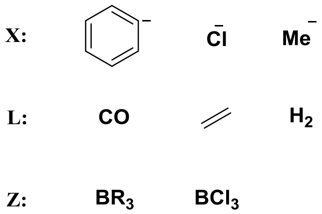


**Figure 3.** Examples of the three types of ligands in the Covalent Bond Classification**.**

Ligands can be classified *via* the Covalent Bond Classification method that divides ligands into neutral L-type ligands (2-electron donors), anionic X-type ligands (2-electron donors) and Z-type Lewis acids (2-electron acceptors)..[21] The knowledge of ligand-metal and substrate-complex interaction have been studied through the characterization of intermediates, determination of crystal structures through X-ray diffraction and the characterization of the complexes by UV-vis, FTIR, EPS and NMR spectroscopy. Both NMR and IR allow for *in-situ* studies of the catalyzed reactions[3] The two spectroscopic techniques have each their advantages with root in the selectivity of the techniques. The sensitivity of NMR towards isotopes with unpaired electrons such as $^{1}$H, $^{11}$B, $^{13}$C, $^{15}$N, $^{19}$F and $^{31}$P to mention some, allow selected nuclei to be studied while ignoring others by choice of experimental conditions. The right experimental conditions can put focus on a species of interest even in small concentrations but low concentration paired with low isotope abundance might cause important intermediates to be undetectable. IR will show the bonding interaction between any unlike atoms and for homogeneous reactions transmission FTIR is the more applicable technique.[3] However, signal overlap can occur and in these cases, data treatment techniques such as deconvolution can be of aid.[22]

**Table 2.** Advantages and disadvantages of homogeneous catalysis.

| Properties of Homogenous Catalysis | Advantage | Disadvantage |
|---|---|---|
| Chemical technology | √ | √ |
| Handling | √ | √ |
| Product separation | | √ |
| Thermal stability | | √ |
| Activity | √ | |
| Selectivity | √ | |
| Mechanistic knowledge | √ | |

Homogeneous catalysis is both a well investigated and an industrially applied discipline. The main advantages mentioned in connection with homogenous catalysts are their activity and selectivity (Table 2), which allow the production of high value-added products, fine chemicals and pharmaceuticals. A less frequently mentioned advantage is the large body of knowledge about homogeneous catalysis that has been derived from the field of organometallic chemistry. The most prominent disadvantages associated with homogenous catalysts is the lack of thermal stability[23] and the difficulty of product separation.

### 1.1.3 Heterogenized Catalysis

To obtain the benefits of both heterogeneous and homogeneous catalysts, the academic community has devoted much attention to the heterogenization of homogeneous catalysts through numerous approaches. These approaches fall within three main categories:

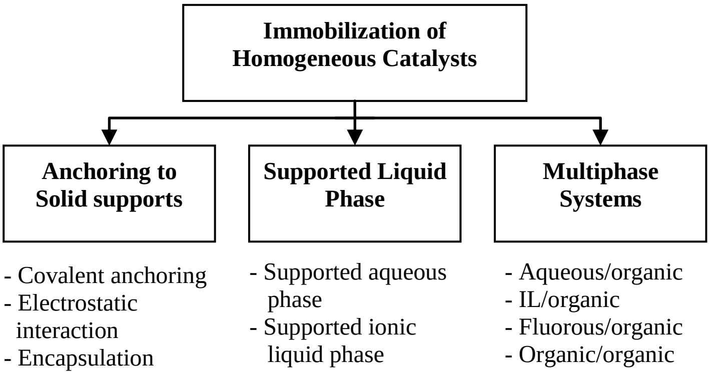


**Figure 4.** Most important approaches for the immobilization of homogeneous catalysts.

#### 1.1.3.1 Anchoring to Solid Supports

The dominant method for heterogenization of a homogeneous catalyst is the attachment of the catalyst to the inner or outer surface of a solid support.[24] Figure 4 lists the most common approaches, which have been utilised to immobilise homogeneous catalysts onto supports. The different strategies are distinguished by the type of interaction between the solid and the support. In the covalent anchoring, surface silanol groups, hydroxy groups or carboxyl groups are utilised as a handle in the functionalisation of the surface with ligand moieties for the complexation of a metal-centre ((i),Figure 5).[25–28] For the electrostatic immobilisation, ligands are tagged with functional groups that enable the electrostatic interaction with an equally surface charged support. Depending on the surface charge of the support positively or negatively charged ligands are applied. Two of the support materials used for this purpose are hydrotalcit (positive surface charge) and montmorillonite (negative charge) ((ii), Figure 5). Other supports applied for electrostatic immobilisation are ion-exchange resins and clays.[29] Very robust catalyst can be obtained through this procedure although appropriate solvents must be selected to maintain the activity of the system.[30,31] The last method to be mentioned here is the encapsulation approach also referred to as “ship in a bottle” ((iii), Figure 5). As the name implies the catalyst is contained in a compartment with small openings retaining the catalyst inside the compartment. These assemblies can be synthesised by either building the support around the catalyst or building the catalyst inside the support cavities. In the case of homogenous catalysts the later route is frequently chosen as the catalyst are instable under the synthesis conditions of inorganic supports.[24,30]

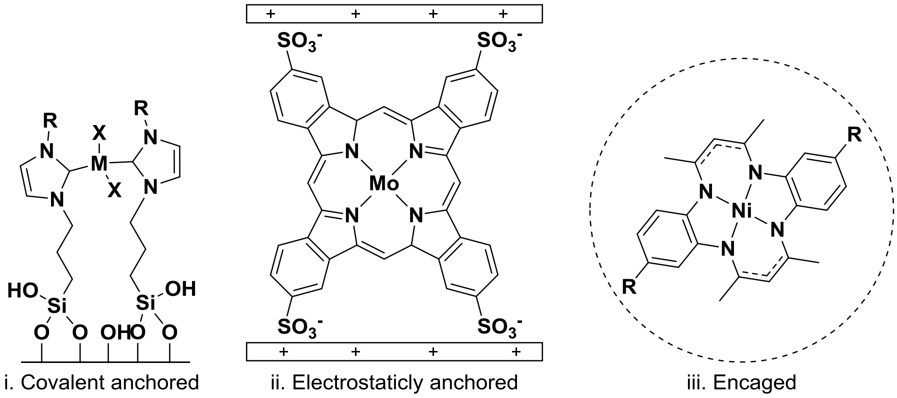


**Figure 5.** Approaches in the anchoring of homogenous catalysts to solid supports.

### 1.1.3.2 Multiphase Systems

This method includes all the systems in which the catalyst and the reactants/products are contained in different liquid phases. The two large benefits of multiphase systems are that the catalyst is truly in a homogenous environment and that catalyst and product can be easily separated. If that is achieved, the reaction can be operated as a continuous extraction.

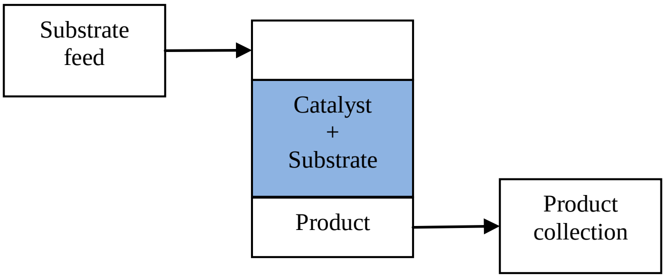


**Figure 6.** Idealised multiphase reaction.

A variety of immiscible solvents systems and solvent specific catalysts have been tailored for case reactions. To immobilise the catalyst in the desired phase, ligands are often functionalised with sulfonate groups or polyether chains for aqueous phase,[32,33] ammonium, sulfonate or imidazolium groups for IL phase,[34–37] perfluoroalkyls for fluorous phase and long alkyl chains for non-polar organic solvents.[38,39] In multiphase systems the immobilisation rely on both van der Waals forces and polarity.

### 1.1.3.3 Supported Liquid Phase

An elegant approach which combine a macroscopic solid catalyst with a microscopic liquid environment is the supported liquid phase consept.[40] In the very first examples, catalysts of this type were prepared by dispersing an aqueous film containing a homogenous catalyst on a solid support.[41] It was quickly realised that the vapour pressure of the aqueous phase was too high for most application and attention was directed towards ionic liquids.[35,42,43]

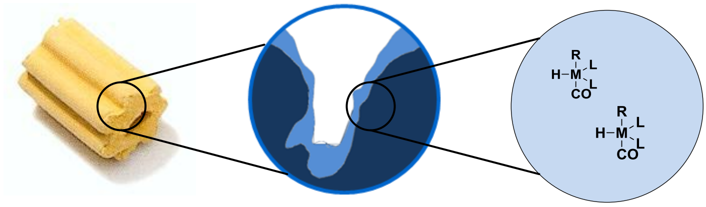
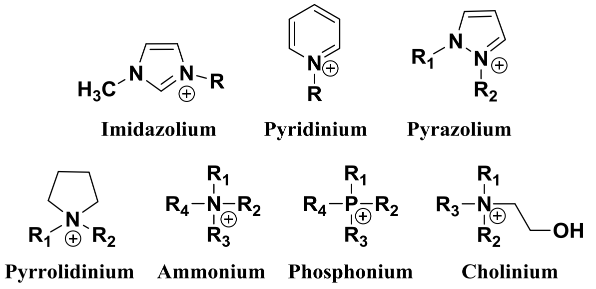


**Figure 7** Schematic view of a supported liquid phase catalyst.

## 1.2 Ionic Liquids

Ionic liquids (ILs) are salts, composed of organic cations and organic or inorganic anions. Ethyl ammonium nitrate, $[(C_2H_5)NH_3][NO_3]$, (m.p.$12^0$C) was the first IL synthesized by Paul Walden in 1914.[44] After this invention, several types of ILs were discovered and some of the common cations and anions of ionic liquids are displayed in Figure 8.[45–50]



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$Cl^-$ , $Br^-$ , $I^-$

$CuCl_2^-$ , $SnCl_2^-$, $AlCl_4^-$

$NO_3^-$ , $PO_4^{3-}$ , $HSO_4^-$ , $SO_4^{2-}$

$CF_3SO_3^-$ , $ROSO_3^-$ , $CF_3CO_2^-$ , $C_6H_5SO_3^-$

$(CF_3SO_2)_2N^-$ , $N(CN)_2$ , $(CF_3SO_2)_3C^-$

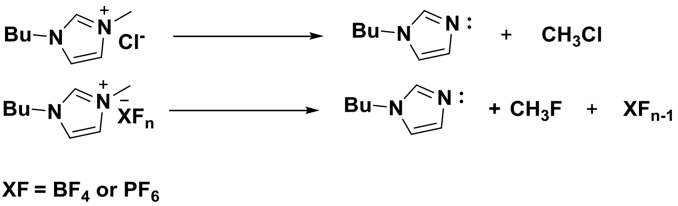
$PF_6^-$ , $SbF_6^-$ , $BF_4^-$

**Figure 8** Common cations and anions of ionic liquids**.**

## 1.2.1 Properties of Ionic Liquids

The melting points (m.p.) of ILs are, per definition, below $100^0$C. ILs with m.p. <$25^0$C, are referred to as room temperature ILs (RTILs). The low melting points of these salts arise from their high molecular entropy. The main contributing factors are the charge distribution on the ions, H-bonding ability, the symmetry of the ions and the van der Waals interactions. Melting points decrease with increased alkyl chain length from methyl to hexyl as a result of changes in the molecular packing.[51–55] Melting points are also affected by the decreasing order of H-bonding ability from $Cl^-$ > $[PF_6]^-$ > $[BF_4]^-$ >>> $[(CF_3SO_2)_2N]^-$ resulting in decreased meting points. [56]

ILs have negligible vapour pressure even at 200-$300^0$C[57] and in some cases thermally stability up to $400^0$C was observed.[58] Decomposition of imidazolium halide based ILs occur through Hoffmann-elimination of the *N*-substituent (Scheme 1). This is essentially a reversal of the $S_N^2$ substitution reaction used to synthesize the quarternary ionic liquids. Decomposition temperatures increase with the decrease of the anion/cation interaction strength in the order $Cl^-$< $[BF_4]^-$ ~ $[PF_6]^-$ < $[(CF_3SO_2)_2N]^-$. The increased stability of ILs containing weakly coordinating anions is most likely due to the higher $pK_A$ of the anions retarding the decomposition of cations according to Scheme 1.[49,53,59,60] The thermal stability with respect to cations of ILs follow a decreasing trend ordered by phosphonium >imidazolium> tetra-alkyl ammonium ≈ pyrrolidinium.[61]



**Scheme 1** Decomposition mechanisms for imidazolium based ILs.

Hydrogen bonding affects the hydrophobicity of ILs which becomes more pronounced with increased charge delocalisation in the order $Br^- \sim Cl^- \sim I^-$> [$BF_4$] > [$PF_6$] > [$(CF_3SO_2)_2N$].[62] Hydrophobic ILs also increase the stability of metallic anions since they protect them from hydrolysis via water segregation.[63–65] Furthermore, the hydrophilic / lipophilic properties of ILs are also key for their application in multiphasic systems.[24]

## 1.2.2 Ionic Liquids in Heterogenized Catalysis

ILs serve several purposes in catalysis. They are good solvents for charged transition-metal catalysts, offering a polar and weakly coordinating environment for the organometallic species, providing additional stability to the catalyst and charged reaction intermediates. Furthermore ILs can act as co-catalysts or independent catalysts due their intrinsic propterties.[43,45,56,66–72]

### 1.2.2.1 Multiphase Systems

Multiphase systems, as immobilisation systems for homogenous catalysts, have the remarkable advantage that the catalyst is located in a homogenous environment and thus their properties and performance are preserved.[24] Maintaining the catalyst a liquid phase separated from that containing the reactants and/or the product offers easy separation of the product and recirculation of the catalyst containing phase with minimum thermal and mechanical stress.[73] The crucial discovery in the development of multiphase catalytic reactions was the development of ligands with hydrophilic groups to be applied in aqueous biphasic systems. The high polarity of ILs enable the use of ligands originally developed for aqueous system,[36,74] when stabilising transition metal complexes in ILs. Furthermore, other types of metal complexes were successfully used as catalysts in ionic liquids. For instance, no leaching was observed for alkyl complexes in phosphonium ILs and carbene-complexes are well retained in imidazolium based

ILs. [35] The tuneable solvent properties of ILs enable the formation of multiphase solvent systems with a range of molecular solvents. The very low vapour pressure of ILs eliminates loss by evaporation and high thermal stability enable process operation in wide temperature window. Lastly, ILs are able to dissolve a variety of organic molecules and both efficient and selective solubilisation have been reported for IL based processes.[24,75]

### 1.2.2.2 Supported Ionic Liquid Phase Technology

Supported ionic liquid phase (SILP) technology is based on an IL thin film containing a homogeneous catalyst, which is uniformly distributed in the pores and on the surface of a mesoporous solid material by physisorption (Figure 9).

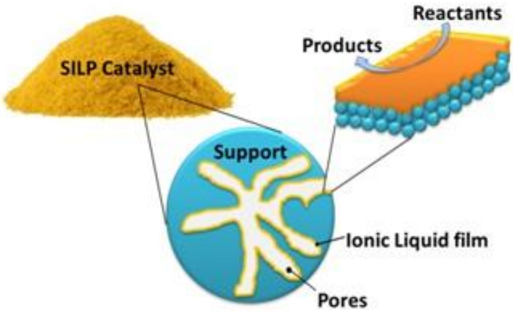


**Figure 9** Principle of SILP catalysis technology.[42]

Distributing the catalyst containing IL onto a solid support is a simple and easy way to optimize the utilization of both the IL and the catalyst compared to a biphasic system. The structure and catalytic activity of the homogeneous catalyst remains, in principle, the same as when dissolved in bulk IL, although the diffusion limitation, sometimes observed in bulk IL, is reduced due to small film thickness and high surface area of the IL film. A SILP catalyst can thus provide the high activity and selectivity of a homogeneous catalyst and the product separation and catalyst recovery usually achieved with an heterogeneous catalysis. The typical IL properties such as negligible vapour pressure, large liquid range window and thermal stability ensure that the IL is retained on the support in its fluid state even at elevated temperatures. It has also been reported that ILs form a solvent cage around the metal complexes that further reduced the mobility of the ions in the ILs, resulting in an increased viscosity of the IL film in the SILP catalyst.[76,77]

The SILP principle was reported independently by Riisager and Mehnert *et al*. for the immobilization of a Rh complex on silica gel using the ionic IL [BMIM][PF$_6$]

and was applied in hydrogenation and hydroformylation reactions.[78–80] Since then, several studies have been reported, mainly for gas-phase reactions in flow reactors.[42]

The solvent properties of the ILs such as hydrophilicity and hydrophobicity, polarity etc. can be tuned using the appropriate cation/anion combination. Together with the intrinsic chemical properties of anion and cation, the solvent properties can enhance catalyst activity and selectivity.[43,69,81] The negligible vapour pressure of ILs avoids removal of the thin film via gas-phase leaching. During catalysis, the gas phase feedstock diffuses inside the pores of the porous support, and dissolves in the IL film in which the metal complex is immobilized. Once the product vapours is released from the IL film it diffuses out of the pores. The product vapour phase should thus have a negligible solubility in the IL film. Gas phase SILP catalyst technology is based on the volatility of the reaction components and is therefore limited to feedstock and products with high vapour pressure.

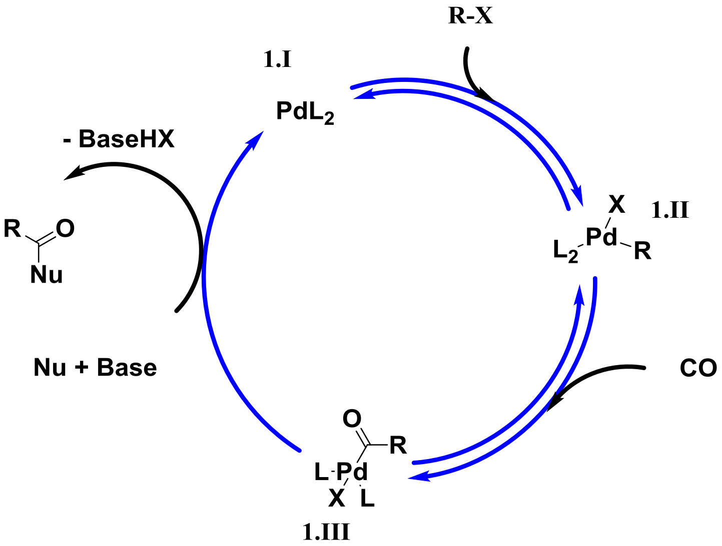
## 1.3 Palladium Catalysed Aminocarbonylation Reactions

In aminocarbonylation reactions, amines can act as base, nucleophile or both. For instance, amines act as nucleophiles in the carbonylation of unsaturated C-C bonds and organohalides or pseudohalides. In carbonylation of organohalides base activation of the nucleophile is required. Both inorganic bases and secondary amines such as pyridine and diethyl amine are frequently applied. Amines that can act as both nucleophile e.g. diethyl amine and DBU, are at times avoided as bases but can also be applied in excess to sacrifice one equivalent as base while one equivalent is used as nucleophile. In the oxidative carbonylation of amines, these reagents act as nucleophiles, but in two sequential nucleophilic attacks.

In the following sections, a brief overview of Pd-catalysed aminocarbonylation reactions will be presented.

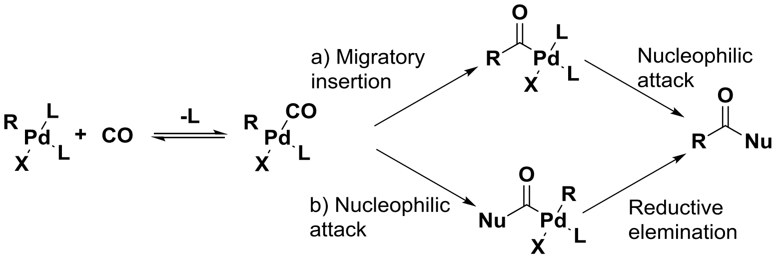
### 1.3.1 Carbonylation of Organic Halides and Pseudo Halides

The carbonylation of halo-arenes was pioneered by Heck in the early 1970's[82,83] and has received much attention due to the interest in incorporating carbonyls in fine chemicals.[19,84,85] The generally accepted mechanism shown in Scheme 2 starts from a Pd(0) complex (**1.I**) with the oxidative addition of an organic halide, followed by CO migratory insertion into the Pd-aryl/alkyl bond to form the intermediate Pd-acyl (**2.III**). Base activation of the nucleophile and nucleophilic attack results in the reductive elimination of the carbonylated product and regeneration of the active species.



**Scheme 2** General mechanism for the carbonylation of organic halides.

Various types of reactants were studied and it has been reported that the use of pseudo halides such as tosylate and mesitylate groups increases the rate of oxidative addition compared to their bromide and chloride analogues, which are generally more readily available. Using amines as nucleophiles, excellent functional group tolerance was observed[86] and application of amines bearing ester groups and aminophosphonates can be applied as N-nucleophile.[87] An alternative mechanism compared to that displayed in Scheme 2, has been proposed to proceed through the formation of a Pd-carbamoyl or Pd-ester complex (Scheme 3, route b) by nucleophilic attack from the amine at the coordinated CO.



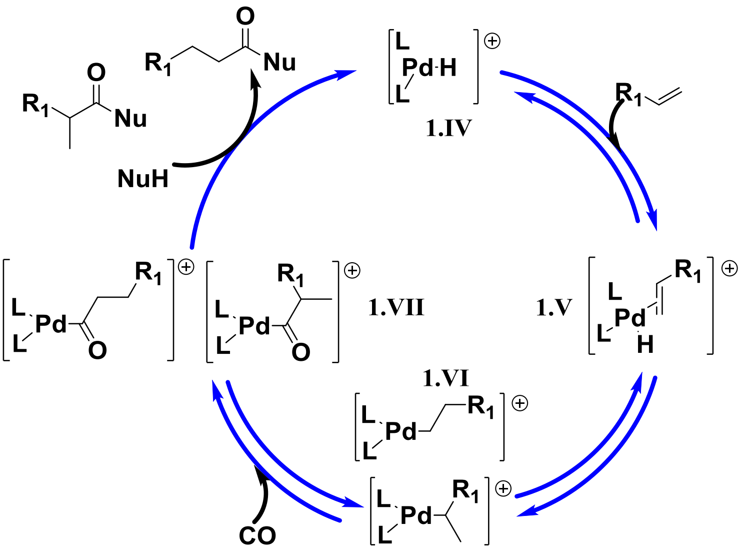
**Scheme 3** Alternative mechanisms for the carbonylation of organic halides.[84]

Nucleophilic attack at the coordinated CO had been observed in alkoxycarbonylation[88] and double carbonylation of aryl halides, involving O-nucleophiles[89] and N-nucleophiles.[90–92] The double carbonylation of organic halides to give ketocarboxamides was long considered a rare reaction requiring high pressure (> 30 bar)[84] but in recent years several publications have shown that this process can be achieved under mild conditions using the appropriate ligand.[92–95]

In these reactions, groups such as diazonium[96] or amine groups[97] have also been used as leaving groups.[84] Of particular interest for this work, the formation of Pd-acyls from aryl amines through C-N bond activation followed by CO migratory insertion has been suggested as intermediates in the formation of amides.[97–100] This type of reaction was investigated in the Chapter 2 and a more detailed description of the current state of the art in this area will be presented in the introduction of this chapter.

## 1.3.2 Carbonylation of Unsaturated C-C Bonds

Acetylene and ethene were the first substrates to be applied in industrial carbonylation reactions[3,101] and many large scale industrial processes involve the carbonylation of an olefin in the presence of a nucleophile.[102–105] The accepted mechanism shown in Scheme 4 starts from a palladium hydride complex (**1.IV**) that coordinates the olefin substrate to form the palladium hydride alkene complex (**1.V**).



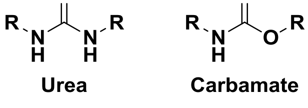
**Scheme 4** General mechanism for the carbonylation of organic unsaturated C-C Bonds.

The following insertion is determinating for the regio- and enantioselectivity selectivity of the reaction with the formation of either the branched or linear alkyl-complexes (**1.VI**). CO coordination and migratory insertion results in the acyl-complex (**1.VII**) and nucleophilic attack at the acyl leads to the formation of the product and regeneration of the active species (**1.IV**). Depending on the electronic and steric properties of the substrate, the alkene insertion step (**1.V→1.VI**) can be reversible, resulting in substrate isomerisation. Especially internal mono-unsaturated olefins are prone to isomerisation, consequently providing the terminal carbonylation product regardless of the starting material.[106–108] For terminal olefins or styrenes both branched and linear carbonylation products can be obtained.[107–111] This difference in reactivity arise from π-benzylic stabilization of the alkene intermediate in the case of styrenes.[112] The bulkiness of the olefin also contributes to the formation of the branched carbonylation product. Only recently have branched alkylamides been obtained[113] despite the interest in branched amides as versatile intermediates and building blocks in chemical, agrochemical and pharmaceutical industry.[105,109]

A number of catalytic systems have been reported for the regioselective carbonylation of olefins and apart from the substrate, the properties of the ligands and the solvent polarity were shown to also affect the reaction.[108,112,113] In the aminocarbonylation of styrene, the use of small cone angle ligands along with polar protic solvents usually favours the formation of the branched product while ligands with large cone angle[108] or bidentate ligands favour the linear amide. In the case of linear olefins, monodentate ligands also favour the formation of the branched product but the use of ammonium salts instead of amines was crucial for the success or the reaction.[113] This underlines the difficulty of stabilizing the Pd-alkene intermediate (**1.V**) for linear olefins.[113]

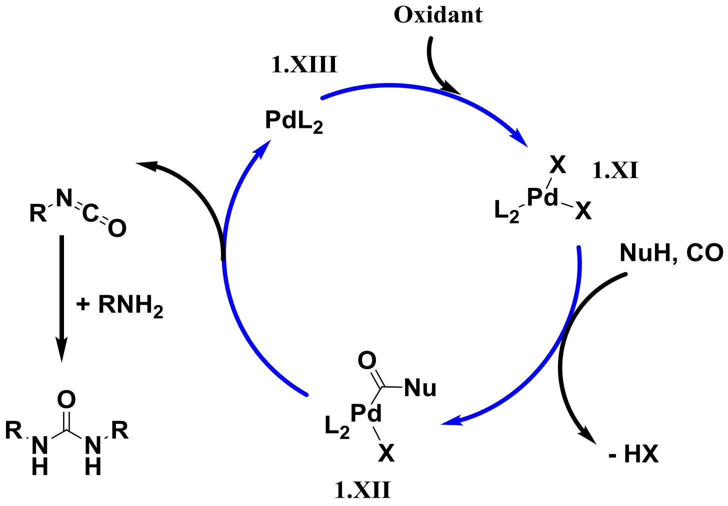
### 1.3.3 Carbonylation of Amines and Nitroarenes

This covers the narrow area of reductive and oxidative carbonylation. The reductive carbonylation involves an *in-situ* formation of amine which undergoes subsequent carbonylation. Two classes of products can be obtained depending on the nucleophile used: ureas and carbamates (Scheme 5).



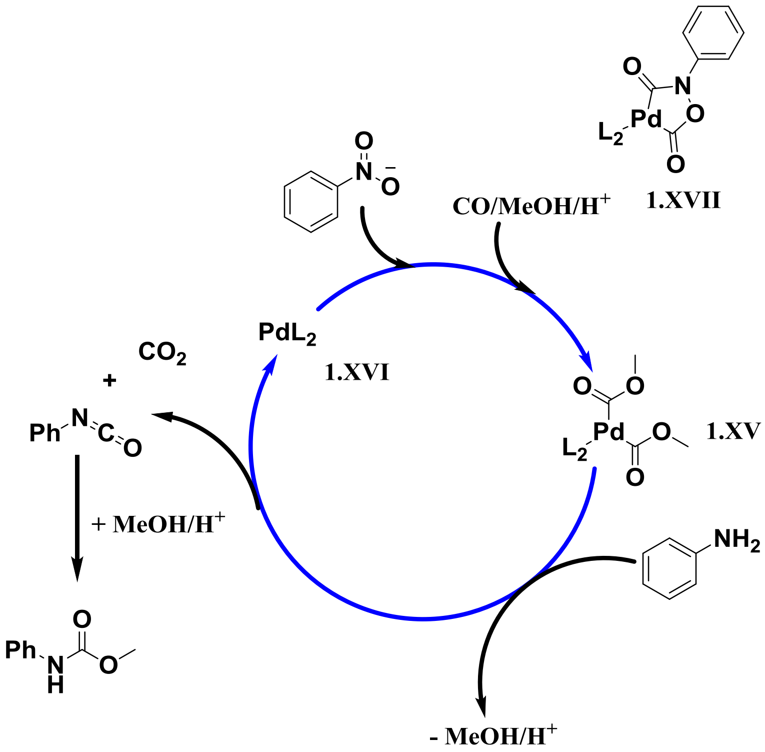
**Scheme 5** Genereric structures of urea and carbamate.

Both can be obtained through the oxycarbonylation or oxidative carbonylation of amines or mixtures of alcohols and amines respectively. For low boiling substrates such as methylamine, the reaction can be performed in gas phase over solid catalysts.[114,115] The carbonylation of substrates with higher boiling points such as higher order amines has to be performed in liquid phase and has no industrial application this far.[102] Nonetheless, the carbonylation of amines is frequently studied with homogeneous catalysts as the products of such a process are relevant for the production of polymers, pharmaceuticals and agrochemicals.[114,116–118] The formation of ureas is expected to follow a mechanism involving two separate nucleophilic attacks, which will be discussed briefly in this chapter.



**Scheme 6** Mechanism for the palladium catalyzed oxidative carbonylation of amines.

A more thorough discussion of the formation of ureas will be presented in Chapter 3. Starting from a Pd(II)-species (**1.XI**, Scheme 6), coordination of CO and amine leads to the formation of the carbamoyl complex (**1.XII**), together with the release of acid.[116] The Pd(0)-species (**1.XIII**) is reoxidised to the active Pd(II)-species by an oxidizing agent. The carbamoyl (**1.XII**) undergoes nucleophile abstraction to release isocyanate. The isocyanate then reacts with a molecule of amine from the solution to form urea.[33] A number of different oxidants have been used for the reactions and Wacker-type catalytic systems have also been reported.[118,119] Improved catalytic systems for the oxidative carbonylation of amines have eliminated the need for an auxiliary metal and oxygen or air is frequently used as oxidant.[117,120–128]



**Scheme 7** Reductive carbonylation of nitrobenzene.

The carbamate is suggested to be formed through nucleophilic attack on the isocyanate and intermediate formation of both isocyanate and urea has been observed. This was suggested to be caused by the *in-situ* decomposition of urea into isocyanate, allowing for the formation of the carbamate as illustrated in Scheme 7.[129] This is supported by the more forcing conditions required for the carbamate formation.[120,130]

The carbonylation route from nitroaryls to carbamates is most frequently explored with nitrobenzene as substrate. This process is also known as reductive carbonylation due to reduction of the nitro compound and no external oxidant is needed. The selectivity towards isocyanate or carbamate is largely controlled through the choice of solvent since reactions performed in sterically accessible alcohols yields carbamate.[131]

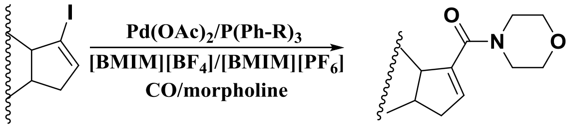
The catalyst is typically stabilised by bidentate N-donor ligands [84,132–134] or mono- or bidentate P-donor ligands[135,136] while N/P-donor ligands are encountered less frequently.[137] The mechanism (Scheme 7) of this reaction is tentative and palladium containing intermediates have proven difficult to isolate.[138–140] The mechanism was suggested to proceed through the *in-situ* formation of aniline and a palladium-diacyl complex (**1.XV**) to release isocyanate and a Pd(0) complex. The aniline formation has not been accounted for, but addition of catalytic amounts of aniline increases the rate of product formation, suggesting that aniline could be formed *in-situ*.[134] The palladacycle (**1.XVII**) has been suggested to be an intermediate in the formation of isocyanate, but was far less active for the formation of the carbamate than the diacyl-complex (**1.XV**).[134] For the formation of ureas stoichiometric amounts of amine are required.[133]

## 1.4 Aminocarbonylation in Ionic Liquids

The application of ILs in aminocarbonylation has been motivated by a number of reaction features which can obtained by the aid of ILs. Among the most frequently mentioned benefits are ease of separation, the low volatility and toxicity of ILs for solvent applications, catalyst separation with unmodified complexes and reaction promoting effects of the IL resulting in improved activity or selectivity. [117,120,141–148] The preferred ILs have been imidazolium and phosphonium (PIL) based ILs due to their higher thermal stability and poor nucleophilisity of the decomposition products.[145,146]

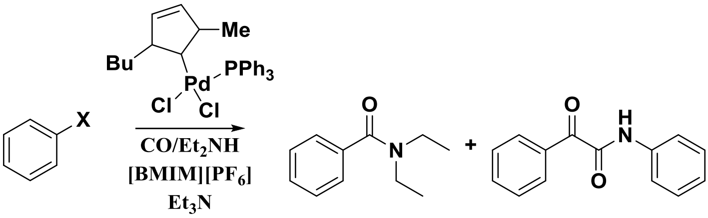
### 1.4.1 Carbonylation of Organohalides

The modification of naturally occurring steroids are of interest in pharmaceutical chemistry due to the altered receptor interaction which changes in stereochemistry or electronic properties of the molecule which a functionalisation may induce.[149] The functionalisation of steroids by aminocarbonylation has been investigated in imidazolium based ILs with secondary amides as nucleophiles. Iodide bearing varieties of adrostene gave the corresponding amides under mild conditions (1 bar and 100°C) according to Scheme 8.



**Scheme 8** Aminocarbonylation of steroid derivatives.

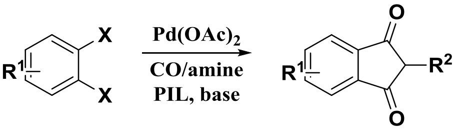
The reaction was carried out in neat IL followed by extraction into toluene. In the first run, full conversion was obtained but the catalyst was observed to deactivate when reused despite the addition of extra ligand. Various phosphine ligands were tested. The use of PPh$_3$ resulted in leaching of the ligand while when the charged phosphine 4-(diphenylphosphino)-benzoic acid was used, leaching was prevented.[141,142] More simple haloarenes have also undergone aminocarbonylation in ionic liquid. The carbonylation of iodobenzene has been performed in a microflow reactor with [BMIM][$PF_6$] as solvent and a Pd-NHC catalyst according to Scheme 9.[143] The effect of pressure in batch and in flow was compared and in all cases higher conversion and selectivity was obtained in flow. Selectivity towards the double carbonylation product dominated in all cases. This was ascribed to the higher gas/liquid surface area obtained in flow, thereby facilitating the diffusion of CO into the liquid phase. The performance of the catalyst/IL mixture after extraction of the product was not examined.



**Scheme 9.** Synthesis of carboxamides and ketoamides in flow.

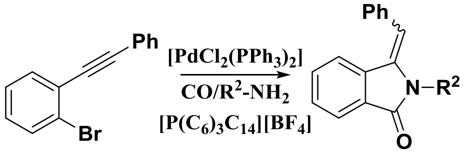
Performing the same reaction in batch and applying $Pd(OAc)_2$/dppf as the catalytic system in trihexyl(tetradecyl)-phosphonium bromide ([$P_{666[13]}$][Br]) as solvent, shifted the selective to formation of the monocarbonylation product.[144]

In the presence of a $Pd(OAc)_2$ 1,2-halobenzenes were transformed into phtalamides in phosphonium based ILs (PILs, Scheme 10) at atmospheric CO pressure. When applying THF as the solvent, no activity was observed while conversion in IL was related to the applied base. Among the screened bases DBU was found to provide the highest activity and selectivity.



**Scheme 10.** Synthesis of phtalamides in phosphonium based ILs.

Up to 90% conversion and full selectivity towards phtalamides could be obtained by optimisation of the IL. The catalytic system could not be recycled but PILs offer a nontoxic alternative to previously applied solvents.[145] More complex structures were obtained through the combined carbonylative ring closure of 1-Bromo-2-(phenylethynyl)benzene derivatives with primary amines (Scheme 11).The reaction was catalysed by [$PdCl_2(PPh_3)_2$] in [$P_{666[13]}$][Br] and good sterioselecivity with consistent preference for the Z-isomer was obtained. [146]

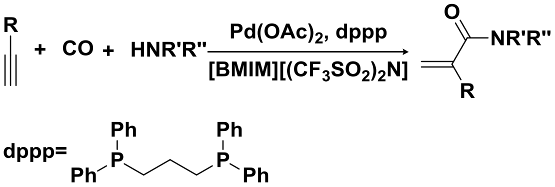


**Scheme 11.** Combined carbonylation and ring closure of 1-Bromo-2-(phenylethynyl)benzene derivatives.

In each of the described reactions the application of ILs have led to improved catalyst lifetime,[141,142] improved selectivity[144,150] or improved reaction safety.[145,146]

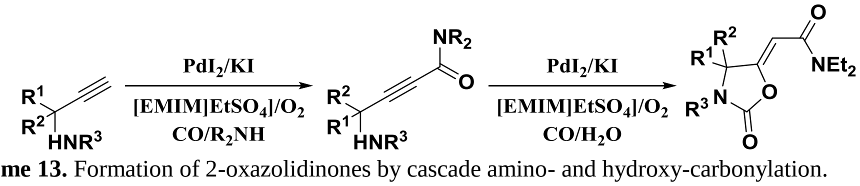
## 1.4.2 Carbonylation of Unsaturated C-C Bonds

The direct synthesis of acrylamides from terminal alkynes have been performed in the imidazolium based IL [BMIM][ $(CF_3SO_2)_2N$] (Scheme 12). The reaction was performed in neat [BMIM][ $(CF_3SO_2)_2N$] under mild conditions (13.8 bar and 110°C), followed by extraction of the into toluene giving the $\alpha$-methylene amide in 85% yield under optimised conditions. The conversion of internal alkynes could also be performed although with lower yields. The catalyst-containing IL could be recycled 5 times without loss of activity or selectivity.[147]



**Scheme 12.** Formation of acrylamide in imidazolium based IL.

The direct synthesis eliminates a reaction step which is a considerable improvement of the procedure. Furthermore the product was formed regioselectively when the reaction was performed in [BMIM][ $(CF_3SO_2)_2N$], thus avoiding the need for separation of the three possible regioisomers. The reaction was also studied with [BMIM][$PF_6$] as solvent and in this case mixed regioisomers was obtained.[147]



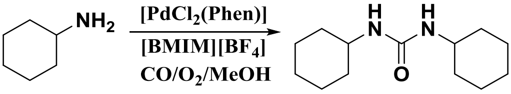
**Scheme 13.** Formation of 2-oxazolidinones by cascade amino- and hydroxy-carbonylation.

The aminocarbonylation of terminal alkynes have also been investigated for a $PdI_2$/KI catalyst system dissolved in [EMIM][$EtSO_4$]. The reaction formed 2-oxazolidinones according to Scheme 13 by two sequential carbonylations. After reaction, the product was extracted with diethyl ether and the IL phase recycled. During five consecutive runs, activity and sterioselectivity was maintained for all the tested substrates.[148]

## 1.4.3 Carbonylation of Amines

### 1.4.3.1 Carbonylation in Multiphase Systems

The limited solubility of some palladium complexes in conventional solvents and the improved sustainability that could be obtained from a recyclable catalytic system has motivated the investigation into oxidative carbonylation in IL. The oxidative carbonylation of amines have been performed in IL system according to Scheme 14. Full conversion to the intended diphenyl urea was obtained although under forcing conditions (40 bar and 140°C). After the reaction, water was added to precipitate the product while the catalyst remained in the IL. Removal of water by distillation enabled the recycling of the catalyst. The reaction was sparingly active without IL most likely due to the poor solubility of the catalyst in organic solvents. [120] The reaction was also catalysed by a $PdI_2$/KI system in neat [BMIM][$BF_4$]. In this instance, the product could be extracted into diethyl ether after reaction and substantially milder reaction conditions (20 bar and 90°C) could be used.[117]

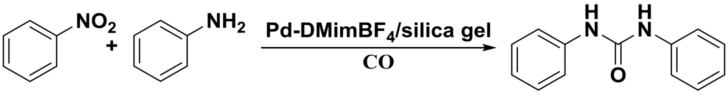


**Scheme 14.** Oxidative carbonylation in of amines in imidazolium based IL.

In the two examples of oxidative carbonylation in ionic liquid recyclable systems have been obtained in both cases.

### 1.4.3.2 Carbonylation on Supported Ionic Liquid Phase

In response to the stabile catalytic system which was obtained under the conditions described in Scheme 14, a Pd-based silica gel confined IL catalyst was applied in the reductive carbonylation of nitrobenzene and aniline (Scheme 15).[151]

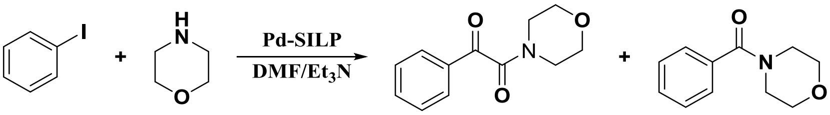


**Scheme 15.** Formation of diphenyl urea by reductive carbonylation.

The catalyst was prepared by one-pot synthesis forming a solid. The catalyst material was applied under solvent free conditions and high temperature and pressure (50 bar and 180°C).

A TOF of 7440 $h^{-1}$ was obtained but extraction of the product from the catalyst material with methanol also led to the removal of the IL and a drop in conversion was observed when the catalyst was recycled.[151]

The carbonylation of iodobenzene in the presence of morpholine was studied using Pd-based SILP catalysts applying [BMIM][$BF_4$] and [BMIM][$PF_6$] as the IL phase (Scheme 16). Under forcing conditions (30 bar and 100°C), full conversion and 96% selectivity to the α-ketoamide could be obtained.



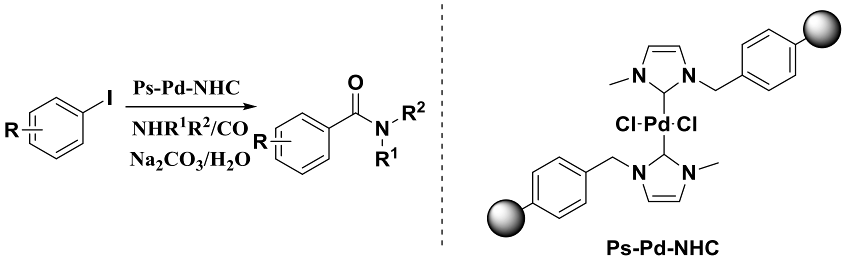
**Scheme 16.** Aminocarbonylation of iodobenzene on SILP.

In this study, the anion was shown to affect the selectivity of the reaction since a slightly more selective catalytic system was obtained using [BMIM][$BF_4$] than with [BMIM][$PF_6$]. During the optimisation of the reaction conditions, it was observed that more polar and coordinating solvents such as DMF resulted in more active catalytic systems and that longer reaction times improved the stability of the catalyst upon recycling and a maximum TON of 333 was achieved during six recycles of 12 hours. At reaction times shorter than 12 hours the [$Pd(dba)_3 \cdot CHCl_3$]/[BMIM][$BF_4$]-SILP was the least stable catalyst examined. Leaching of palladium into the reaction mixture was observed for all the tested catalysts. Applying the catalyst to other secondary amines, selectivity appeared to be affected by both steric and electronic properties while bulky amines resulted in lower conversions. . Unfortunately no characterisation of the spent catalyst was performed.[74]

Even though the aminocarbonylation of iodobenzene has been performed successfully in bulk IL it was not possible to repeat these results using SILP catalysts. In both of the reactions mentioned above, the IL was observed to leak from the catalyst material and only under certain conditions could a stable catalyst be obtained in the case of aminocarbonylation of iodobenzene.

### 1.4.3.3 Solid Supported Homogenous Catalysts

In the case of aminocarbonylation, homogeneous catalysts supported on solids by other means than SILP have been investigated to a greater extent. Iodoarenes have been the substrate of choice and the formation of amides and α-ketoamides have been studied with Pd-complexes with P,[152–155] S,[156] Se[157] and N[158] containing ligands that were supported on polymers,[154,158] silica[152,153,155–157,159] and zeolites.[160] Palladium-carbene functionalised polystyrene (Ps-Pd-NHC)[161] has been applied for the aminocarbonylation of iodoarenes in water under mild conditions (100 psi and 100°C, Scheme 17 ).[158] After reaction, the catalyst was removed by filtration, washed and dried before recycling. Good functional group tolerance was observed for the iodoarene substrate while the reaction was more sensitive to the nature of the amine.



**Scheme 17.** Aminocarbonylation of iodoarenes over polystyrene supported palladium carbene.

*o*-aminopyridine and and *m*-aminopyridine was also tolerated as nucleophiles although a steep decrease in yield was observed for *o*-aminopyridine. The dried catalyst material was recycled 4 times without loss of activity or selectivity. The product phase was analysed by ICP-AES and the palladium content was found to be below the detectable limit (0.01 ppm). $Pd(OAc)_2$ was applied in a homogeneous test reaction under identical conditions and similar activities were observed for the two catalysts.

The aminocarbonylation of iodoarenes to form amides was also investigated using [$PdCl_2$(Phen)] encaged in Y zeolite ($PdCl_2$(phen)@Y) under more forcing conditions (20 bar and 130°C). Recyclability was compared for two heterogeneous catalysts (Pd/Y and Pd/C) and two solid supported homogenous catalysts ($PdCl_2$(phen)@Y and [$PdCl_2$(phen)] adsorbed on Y zeolite). Similar conversion was obtained for all catalysts in the first run but only $PdCl_2$(phen)@Y preserved activity during 16 runs. The fresh and spent catalyst were analysed by XPS. Spectra of the fresh $PdCl_2$(phen)@Y catalyst contained signals corresponding to N, C, Cl and Pd binding energies characteristic for the [$PdCl_2$(phen)] complex. After the first run, only signals corresponding to Pd(0) were observed and the Cl signal was absent. Hot filtration experiments indicated the formation of stable nanoparticles. Interestingly, the signal assigned to the Ns binding energy gradually decreased in intensity with the number of recycles.[160]

Limiting the substrate scope to iodobenzene the aminocarbonylation was investigated with Pd-phosphine functionalised mesoporous silica materials.[162] The solid supported catalyst was prepared by grafting Pd-complexes of (triethoxy)silylpropyl tagged phosphines onto SBA-15 mesoporous silica (Figure 10).

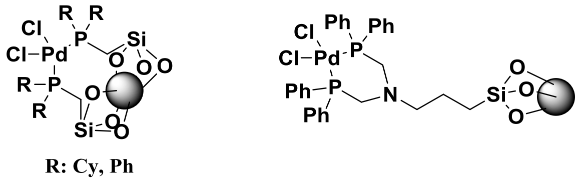


**Figure 10.** Silica grafted complexes applied in aminocarbonylation of iodobenzene.

The prepared catalyst was compared to commercially available heterogeneous catalysts and was found to outperform these with respect to conversion but full selectivity towards the desired $\alpha$-ketoamide was only obtained with the heterogeneous Pd/Y-catalyst. In three consecutive recycles, the catalyst exhibited no significant loss in activity or change in selectivity although a decrease in the activation time was observed for the second and the third run, which was ascribed to the formation of small and well dispersed nanoparticles.[152] Hot filtration experiments indicated a homogenous mechanism relying on the leaching of palladium during catalysis. Similar results were obtained with bidentate phosphines.[153]

Similar results were obtained using Pd-complexes with S,[156] Se[157] or N[158] containing ligands supported on silica[152,153,156,157,163] and MCM-41.[155]

In conclusion, the Y-zeolite confined catalyst and the polymer supported carbene stand out as the only stable catalysts but displayed rather low activities.

A recent review by de Vries *et al.*[23] on covalently bonded solid supported homogeneous catalysts for metathesis, Heck- and hydrogenation reactions described the same trends.[23] These findings led the reviewers to discourage further publication of solid supported homogeneous catalysts, and encourage research into catalyst decomposition. They also listed a number of catalyst-characterisation best-practice measures. However, the aim to develop catalyst for continuous flow production of platform chemicals within fine chemical and pharmaceutical synthesis under mild and safe conditions remains valid. For homogenous catalyst to be applicable in such processes both very active and very stable catalysts are required. These aims have been achieved with biphasic or SILP systems.[102,164]

## 1.5 Objectives

The aim of this thesis is to study palladium catalyzed aminocarbonylation reactions and the influence that the application of ILs as solvent or co-catalysts may have on the activity and selectivity of these reactions. The effect of physical reaction parameters and the stabilizing effects of ligands and ILs on the catalyst are examined with the principal aim to improve the understanding of the reaction mechanism. This serves the purpose of a rational ligand design and reaction optimization.

The specific objectives organized by chapter can be summarized as follows:

### Preparation of Benzamides by Carbonylation of Anilines

- To study a new, simple and robust synthesis procedure for the formation of benzamide.
- To study the ligand effect on catalytic performance

### Palladium Catalyzed Carbonylation of Anilines in Ionic Liquid

- To optimize the physical parameters of the reaction.
- To evaluate the influence of several oxidants and ionic ligands on the output of the reaction.
- To shed further light on the mechanism of the reaction through high pressure NMR-experiments.

### Oxidative carbonylation of Aniline in Continuous Flow

- To synthesise and characterise a solid supported catalyst for continuous liquid phase conditions by application of Supported Ionic Liquid Phase technology.
- To study the influence of ligands and supports on catalyst activity and stability.

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# Chapter 2

# Preparation of Benzamides by Carbonylation of Anilines

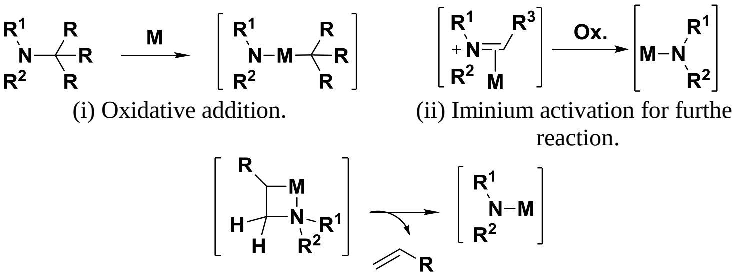
# Preparation of Benzamides by Carbonylation of Anilines

This work was performed in collaboration with Jan Lorkowski, Uniwersytet im. Adama Mickiewicza w Poznaniu.

## 2.1 Introduction

### 2.1.1 Activation of C-N Bonds

The activation of C-N bonds has recently received attention as a parallel and complementary tool to C-X and C-H bond activation[1,2] since this process could give access to new synthetic pathways in organic synthesis.[3] With transition-metal catalysis in rapid development, this bond activation reaction already yielded impressive results.[4] The activation of C-N bonds have recently been reviewed.[1,2,5]



(i) Oxidative addition.

(ii) Iminium activation for further reaction.

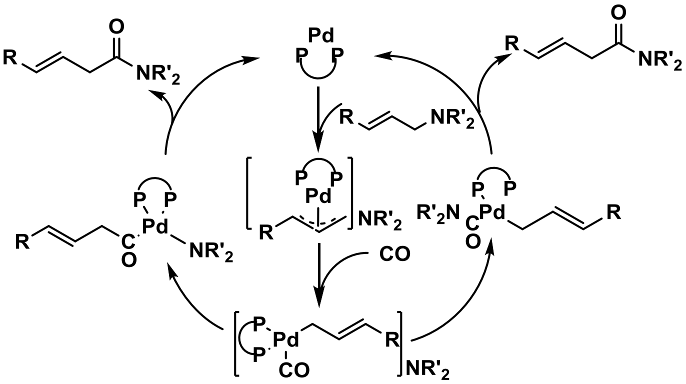
(iii) ß-N elemination.

**Scheme 1.** Three general mechanisms for the C-N activation.

To date, three mechanisms have been proposed for this transformation (Scheme 1): (i) Oxidative addition to low-valent late transition metals, (ii) iminium activation and (iii) ß-N elimination.[1] This chapter will focus on the catalytic oxidative addition of amines.

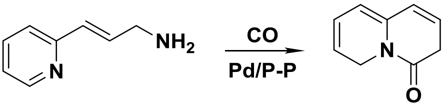
The oxidative addition of primary amines is a challenging reaction due to the inertness of C-N bonds. For instance, the length of an aryl-$NH_2$ bond is on average 1.35 Å while that of an aryl-F is ca. 1.36 Å and that of an aromatic C-H bond is approximately 1 Å.[6] However, the C-N bond becomes significantly elongated upon formation of an ammonium group (to an average of 1.465 Å), which thus constitutes a significant activation. Moreover, the size and polarisability of the ammonium-group, make this group a good leaving group.[2] In this context, the activation of C-N bonds is usually performed via Brønsted[5,7–10] or Lewis acidsactivation.[8,11–13]

The oxidative addition of amines is most commonly performed with allylamines where the reaction intermediate can be stabilised through the formation of allyl-Pd complexes. For this particular kind of reaction, allylic amines have become an important class of pseudo-halides.[2] The oxidative addition of secondary [14,15] and tertiary amines were also reported.[16–26] Similarly to primary amines, secondary amines are usually acid activated and/or used as allylic substrates.[27,28]



**Scheme 2** Proposed mechanism for the carbonylation formation of benzamide.[16]

Huang et al.[23] and Murahashi et al.[16] have investigated the carbonylation of tertiary allylic amines without acid co-catalyst. Murahashi reported the synthesis of ß,γ-unsaturated amides from the corresponding allylamines. The mechanism (Scheme 2)[16] was proposed to proceed through oxidative addition of the amine with formation of an allylic-Pd complex, CO coordination and insertion to give the acyl-palladium complex followed by nucleophilic attack by the amide ligand. The reactions performed in ethanol yielded ethyl hept-3-enoate, therefore indicating that the involvement of an acyl-intermediate. However, in the absence of alcohol, the amide formation via a carbamoyl-intermediate could not be excluded.[16]



**Scheme 3** Formation of quinolizinones from pyridyl-substituted allylamine.[23]

Huang et al. reported the synthesis of quinolizinones through the carbonylation of pyridyl-substituted allylamines (see Scheme 3), with good functional-group tolerance on the pyridyl, while dialkylamines were preferred as leaving groups. The reaction was proposed to follow the mechanism proposed by Murahashi et al. In their study, Huang et al. reported an increased stabilization of the allylic intermediate due to the coordinating ability of the pyridyl nitrogen.[23] Both groups reported a large effect of the phosphine ligands: little or no activity was observed with monodentate phosphines while the activity and selectivity of the reaction was greatly affected by the bite angle in bidentate palladium-phosphine complex. This effect has no clear origin but allylic stabilisation of the intermediate comples was mentioned an important factor in the reaction. This was supported by the observed tendency that superior activity was obtained with substrates forming sterically protected allyls.[16] The transformation of pyridyl-allylamines proceeded selectively to quinolizinones and Xantphos was found to give the most active catalytic system.[23] Applying N,N-diethyl-2-hexenylamine as substrate the highest selectivity was obtained with DPPB as ligand while DPPP resulted in a significant formation of alternative products, among other dienes.[16]

Oxidative addition of aryl-amine C-N bonds to transition-metals under catalytic conditions have, to the best of our knowledge, only been studied for Rh-complexes.[24,27–30] Stoichiometric reactions furnished by palladium are published but to a much smaller extend.[31,32] The Rh-catalyzed reactions have been investigated with primary, secondary and tertiary aryl-amines with ortho-acyl[27–30] or ortho-amide substituents.[24] In a resemblance to C-H activation the ortho-substituents have been observed to coordinate directly to the metal center.[28]

### 2.1.2 Preparation of Benzamides from Anilines

Developed strategies to obtain benzamides can be divided into two approaches. One involves the direct breaking of the ($sp^2$)C-N bond of unactivated anilines as discussed above.[31–33] The other method involve the activation of C-N bond by preparation of diazonium salts from anilines which can undergo oxidative addition to palladium.[34,35] This method has been widely applied even in large scale process[36] and was recently adapted for the synthesis of benzamides by *in-situ* formation of the required diazonium spicies.[37]

Although the utilization of diazonium salts have many applications, this approach suffer from three main disadvantages, e.i. the need for stoichiometric amount or even excess of a diazotization reagents such as *tert*-butylnitrite, the sensitivity of the reaction towards moisture as well as the handling of residual diazonium intermediates which can be explosive.[38,39]

A selective and functional-group tolerant method for the synthesis of benzamides from anilines in the absence of additives, the need for inert atmosphere or dried solvents, is therefore desirable.

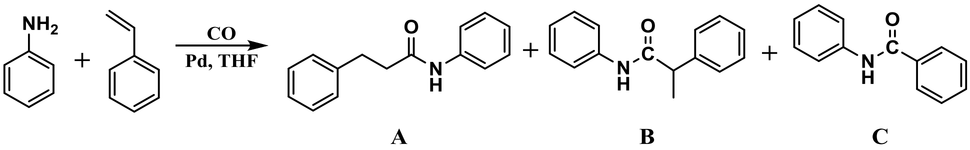
## 2.2 Results and Discussion

Initially, our investigation was focused on the aminocarbonylation of styrene in the presence of aniline. Studies on palladium catalysed aminocarbonylation of olefins are usually reported using phosphine ligands and in many cases, the presence of an acid is required.[40–43] In an interesting report by Dyson *et al.*, Pd/monophosphine systems was observed to catalyse the regioselective formation of amides without added acid.[44]

Initially, some experiments were performed with $PPh_3$ as ligand (Table 1). First, the reaction was carried out under the conditions reported by Dyson *et al.* (entry 1).[44]. The results obtained were in accordance with those reported. A brief study on the effect of the reaction conditions was then performed. When the reaction temperature was lowered to 90°C, an increase of the regioselectivity to the branched product B was observed (entry 2). However, when the catalyst loading was lowered from 5 to 2.5 mol%, no activity was observed. An increase in the styrene/aniline ratio from 10 to 16.5 (entry 4) restored some activity (40% conversion) but greatly affected the chemoselectivity of this reaction since the benzamide product C was formed (33% selectivity) (entry 4). Although fully selective aminocarbonylation of olefins can be challenging to obtain,[40–43] benzamides were not previously reported as by-product in this reaction. In view of this result, the styrene / aniline ratio was lowered to 1 and under these conditions and 50% selectivity to the benzamide was obtained (entry 5). The reaction was then performed in the absence of styrene and total selectivity to the benzamide product C was obtained (entry 6).

In view of these results, the aim of our investigation was changed and we decided to explore the production of benzamide from aniline and CO.

**Table 1.** Substrate and complex effect on the reaction.[a]

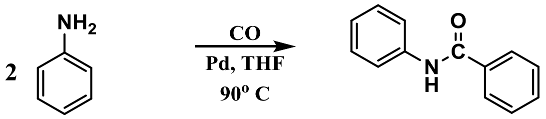


| Entry | Catalyst | Time (hours) | Pd (mol%) | Aniline:Styrene ratio | Conversion[b] (%) | A:B:C[b] (%) |
|---|---|---|---|---|---|---|
| 1[c] | **1** | 2 | 5 | 1:10 | 99 | 8:92:0 |
| 2 |  | 2 | 5 | 1:10 | 99 | 0:100:0 |
| 3 |  | 2 | 2.5 | 1:10 | trace |  |
| 4 |  | 2 | 2.5 | 1:16.5 | 40 | 0: 66:33 |
| 5 |  | 16 | 2.5 | 1:1 | 29 | 0: 50:50 |
| 6 |  | 16 | 2.5 | 1:- | 99 | 0:0:100 |

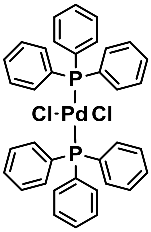
[a] Reaction conditions: 0.3 mmol aniline, 2.5 mol% [$PdCl_2(PPh_3)_2$] with respect to aniline, 0.03 mmol mesitylene, 50 bar CO, 6 mL THF, 90°C, 2 hours. [b] Calculated on basis of GC with mesitylene as internal standard. [c] Reaction temperature was 125°C.

Next, the effect of the ligands was investigated (Tables 2 and 3). The use of the N-heterocyclic carbene iPr was tested using two distinct precursors: the monomeric PEPPSI complex **2** and the dimeric complex **3** (Table 2) and the results compared with those obtained with the [$PdCl_2(PPh_3)_2$] precursor **1**. The reactions were performed at 90°C for 6h under 50 bar of CO and using THF as solvent. In all cases, excellent conversions were obtained with full selectivity to the benzamide product.

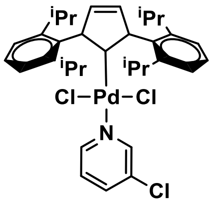
**Table 2.** Effect of the ligand in the formation of benzamide from aniline.[a]



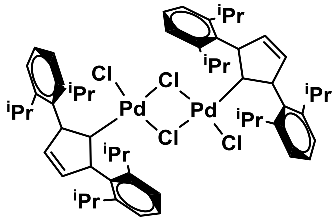
C



1



2



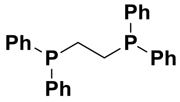
3

| Entry | Pd | Time<br>(hours) | Conversion[b]<br>(%) | Selectivity[b]<br>(%) |
|---|---|---|---|---|
| 1 | **1** | 6 | 92 | >99 |
| 2 | **2** | 6 | 93 | >99 |
| 3 | **3** | 6 | 97 | >99 |

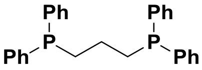
[a]Reaction conditions: 0.3 mmol aniline, 2.5 mol% Pd, 0.03 mmol mesitylene, 50 bar CO, 6 mL THF, 90°C. [b]Calculated on basis of GC with mesitylene as internal standard.

Next, the bidentate phosphine ligands **L1-L4** were tested under the same conditions (Table 3). Bidentate ligands **L1-L3** afforded very low conversions under the conditions used (Table 3, entries 1-3), which is in accordance with literature. On the other hand, when the P-C-P-pincer ligand **L4** was used (entry 4), 62% conversion and full selectivity towards the formation of N-phenyl-benzamide was obtained after 4 hours of reaction.

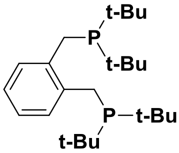
**Table 3.** Testing of bidentate phosphine ligand on conversion and selectivity.[a]



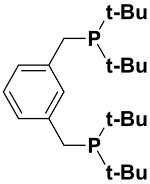
**L1**



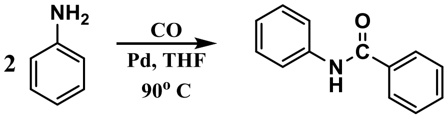
**L2**



**L3**



**L4**



**C**

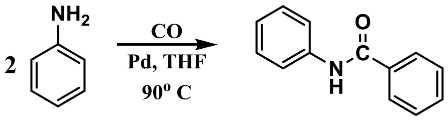
| Entry | Ligand | Time (hours) | Conversion[b] (%) | Selectivity[b] (%) |
|---|---|---|---|---|
| 1 | **L1** | 2 | trace | >99 |
| 2 | **L2** | 2 | trace | >99 |
| 3 | **L3** | 4 | trace | >99 |
| 4 | **L4** | 4 | 62 | >99 |

[a] Reaction conditions: 0.3 mmol aniline, 2.5 mol% $PdCl_2$(COD), 2.5 mol% ligand, 0.03 mmol mesitylene, 50 bar CO, 6 mL THF, 90°C, 6 hours. [b] Calculated on basis of GC with mesitylene as internal standard.

The results described in Tables 2 and 3 clearly demonstrated that both aryl groups of the N-phenylbenzamide originated from the aniline substrate.

At this point, further optimisation experiments were conducted using the ligand **L4** (Table 4). When the reaction was performed under lower CO pressure (30 bar, entry 1), only traces of the product were detected even after 16h of reaction, revealing a crucial role of the CO pressure in this process. When the Pd loading was lowered to 1 mol%, 54% conversion was obtained after 16h of reaction (entry 2). The use of a more coordinating solvent such as MeCN (entry 3) also led to decrease in activity since 87% conversion was measured after 16h. This was most likely caused by competitive coordination of the substrate and the solvent to the Pd centre. When $[Pd(acac)_2]$ was used as a Pd-precursor, a small drop in yield was observed compared that obtained with $[PdCl_2(COD)]$. Such an observation indicates that formation of the active catalyst was slower, but that the chloride ion was not involved in the catalytic cycle under the applied conditions.

**Table 4** Optimisation of the reaction conditions.[a]



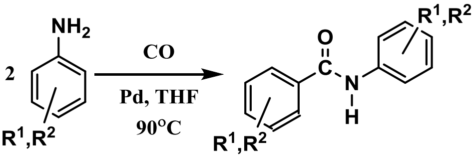
**C**

| Entry | Catalyst | Pd loading (mol%) | $P_{CO}$ | Time (hours) | Conversion[b] (%) |
|---|---|---|---|---|---|
| 1 | $[PdCl_2(COD)]$ /**L4** | 2.5 | 30 | 16 | Trace |
| 2 | $[PdCl_2(COD)]$ /**L4** | 1 | 50 | 16 | 54 |
| 3[c] | $[PdCl_2(COD)]$ /**L4** | 2.5 | 50 | 16 | 87 |
| 4 | $[Pd(acac)_2]$/**L4** | 2.5 | 50 | 6 | 91 |

[a]Reaction conditions: 0.3 mmol aniline, 2.5 mol% Pd, 2.5 mol% ligand, 0.03 mmol mesitylene, 50 bar CO, 6 mL THF, 90°C. [b]Calculated on basis of GC with mesitylene as internal standard. [c]Solvent was MeCN.

With optimized conditions in hand, a series of benzamides with different substituents were synthesized using either $[PdCl_2(COD)]$/**L4** or $[PdCl_2(IPr)]_2$ **3** as catalyst precursors. Although for simple N-phenylbenzamides (Table 5, entry 1), 6 hours was found to be sufficient to reach stoichiometric conversion, longer reaction times were required for substituted anilines and the reactions were performed for 16h (Table 5, entries 2-8). Using $[PdCl_2(COD)]$/**L4** as catalytic system, anilines bearing both electron electron donating (entries 2-3) and withdrawing groups (entries 4-7) in *para* position of the aniline phenyl ring were quantitatively and selectively converted into the corresponding benzamides. Full separation of the catalyst was, on the other hand, non trivial. Furthermore, quantitative conversion was obtained when applying sterically accessible or moderately hindered substrates (Table 5, entries 1-8). However, when sterically hindered *ortho*-substituted substrates 2-methylaniline and 2,6-dimethylaniline, very low conversions (6% and 7% respectively) were achieved in 16 hours (entries 9 and 10). To overcome this problem, $[PdCl_2(IPr)]_2$ **3** was used as Pd precursor and provided 80% spectroscopic yield in the synthesis of 2-Methyl-N-(2-methylphenyl)benzamide (Table 5, entry 9). Moreover, with the highly hindered 2,6-dimethylanline, only 14% conversion of the substrate was observed and the selectivity was switched towards the benzoic acid derivative (Table 5, entry 10).

**Table 5.** Substrate scope of the carbonylative benzamide synthesis.



| | | | [PdCl2(COD)]/L4 | | [PdCl$_2$(IPr)]$_2$ |
|---|---|---|---|---|---|
| Entry | Aniline | Time (hours) | Conversion[b] (%) | Yield[c] (%) | Conversion[b] (%) |
| 1 | $R^1$, $R^2$=H | 6 | >99 | 93 | |
| 2 | $R^1$=*p*-MeO, $R^2$=H | 16 | >99 | 77 | |
| 3 | $R^1$=*p*-Me, $R^2$=H | 16 | >99 | 85 | |
| 4 | $R^1$=*p*-Cl, $R^2$=H | 16 | >99 | 72 | |
| 5 | $R^1$=*p*-Br, $R^2$=H | 16 | >99 | 67 | |
| 6 | $R^1$=*p*-F, $R^2$=H | 16 | >99 | 84 | |
| 7 | $R^1$=*p*-I, $R^2$=H | 16 | >99 | 52 | |
| 8 | $R^1$, $R^2$=*m*-Me | 16 | >99 | 82 | |
| 9 | $R^1$=*o*-Me, $R^2$=H | 16 | 6 | 6 | 80 |
| 10 | $R^1$, $R^2$=*o*-Me | 16 | 7 | 7 | 14* |
| 11 | $R^1$, $R^2$=H, N-Me | 16 | trace | trace | trace |

[a] Reaction conditions: 0.3 mmol aniline, 2.5 mol% Pd, 2.5 mol% ligand, 0.03 mmol mesitylene, 50 bar CO, 6 mL THF. [b] Calculated on basis of GC with mesitylene as internal standard. [c] Isolated yield. *Product was benzoic acid.

The formation of 2,6-dimetylbenzoic acid could suggest the formation of an acyl-intermediate which undergo nucleophilic attack in the presence of water. Attempts to convert N-methyl aniline were unsuccessful regardless of the ligand applied (Table 5, entry 11). GC-MS analyses of reaction mixtures showed appearance of benzoic acids as well as benzenes and phenyl-isocyanats in levels <1%. The benzene derivatives were only observed in the presence of phenyl-isocyantate and in all cases the substitution indicated that the source of these by-products was the applied anilines. The fact that longer reaction times were needed for both substrates bearing electron donating and withdrawing groups was surprising and could suggest a change in mechanism depending on the electronic properties of the substituents. Lower conversions as a consequence of steric hindrance is a commonly occurring observation but the steep change in conversion which was observed when switching catalyst from the formed Pd(II)/**L4** to **2** indicate a high degree of steric crowding on the catalytically active species when palladium was stabilised by **L4**.

### 2.2.1 Mechanistic Discussion

The starting point of this investigation was the aminocarbonylation of styrene and firstly, a [$PdCl_2(PPh_3)_2$]-catalysed system was applied resulting in good selectivity when applied under the conditions used in literatur.[44] During the optimization of the reaction, it was observed that lowering the temperature and the palladium loading lead to a competition between the formation of carboxamide and N-phenyl benzamide. This was rather surprising since several examples of aminocarbonylation of olefins under mild conditions and with similar catalysts were previously reported.[40,41,45,46] These systems involve additives which might favour the formation of the active catalytic species.

Under the applied reaction conditions, [$PdCl_2(PPh_3)_2$] was found to be active in both transformations and competition between the two reactions occurred. This selectivity could be shifted by changing the amount of styrene (Table 1, entries 3-6). Aminocarbonylation of amines generally involve the use of co-catalytic acid[37,40,43,46–48] and the formation of palladium-hydride species in the absence of acid has been proposed to require halogen bearing palladium precursors[44] which are not required in the formation of benzamide. Reactions performed with halogen free precursors (Table 4, entry 4), lead to the selective formation of benzamides. Further investigation of the reaction mixture by Electro Spray Ionization Mass Spectrometry did not lead to the observation of palladium hydride species.

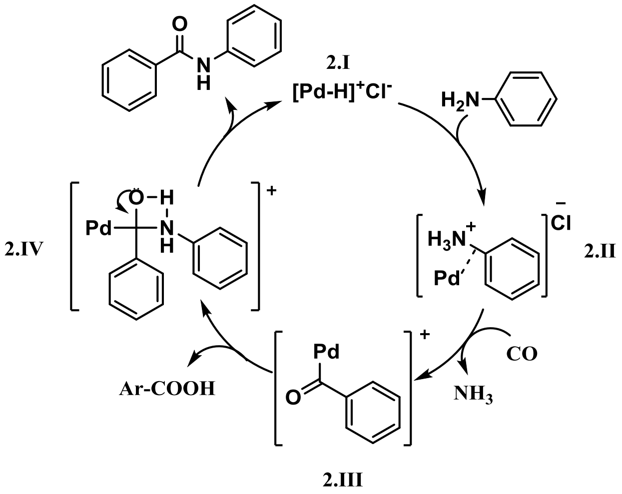
In work by Murahashi *et al.*,[16] deamination of the substrate was observed to take place. Under our applied the conditions, deamination would lead to the formation of ammonia. To determine if ammonia was formed under the conditions applied in the present work, the gas phase found in the reactor after reaction, was bubbled though milli-Q water, as detailed in the experimental section. The water was subsequently subjected to a known colourmetric test[49] which clearly identified ammonia in the solution.

During the investigation of the formation of benzamide, benzoic acid was identified in trace amounts in all but the most active experiments. This is interesting firstly because condensation of benzoic acid with aniline is a well known procedure in the formation of benzamide and secondly because higher activity for the formation of benzamide was observed when the reaction was performed in standard solvent than when the reaction was performed dried solvent. This observation was repeated when catalytic amount of water was added to dry solvent.

The ligand screening revealed a distinct difference between the three ligands providing active complexes: Complex **1** was active in both aminocarbonylation of styrene and in benzamide formation wheras Pd(II)/**L4** and **3** were only active in benzamide formation.

This led to three hypothesises: That the benzamide was formed from a cationic Pd-H active species (Scheme 4), that the benzamide was formed starting from a Pd(0) active species (Scheme 5) or that the product of the catalytic cycle was benzoic acid and the benzamide formed through condensation (Scheme 6).

The first proposed mechanism is initiated by a cationic Pd-H species (**2.I**). The first step in the reaction is the base abstraction of the hydride by the aniline. The formation of the corresponding ammonium in turn activates the C-N bond for oxidative addition to the Pd-centre (**2.II**). CO addition and insertion into the Pd-aryl bond lead to the formation of the cationic Pd-acyl complex **2.III.** At this stage nucleophilic attach from either water or aniline result in the formation of benzoic acid or **2.IV**, respectively. Rearrangement of complex **2.IV** leads to elimination of benzamide and reformation of the active Pd-H.

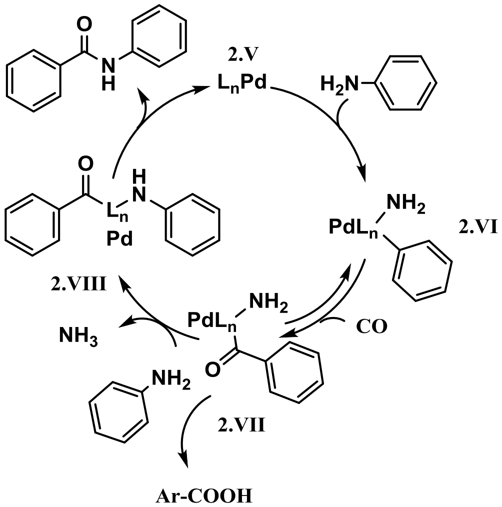


**Scheme 4. Proposed hydride mechanism for the formation of benzamide.**

Metal hydrides are generally considered as bases and alkalimetal hydrides are applied as such. In the case of transition metal hydrides the picture becomes more complicated as additional ligands also affect the properties of the hydride. Cationic palladium phosphine complexes have been observed to form acidic hydrides [50–55] Complexes of this type would furnish the activation of the aniline through ammonium formation which is the principal route in oxidative C-N bond addition[1,2,5] and thus be an ideal starting point for C-N bond activation. Similarly

Pd-H hydrides are the starting point of the aminocarbonylation of olefins as discussed in Chapter 1. This would account for the competition between the two reactions and the difference observed in selectivity between the applied complexes: The more acidic the hydride of a given complex is, the further displaced towards ammonium would the acid-base equilibrium be. In the literature, cationic Pt-H, Pd-H and Ni-H complexes have been reported to have equal acidity for equivalent complexes, while the palladium species have the best hydride donor properties.[51,56] Acidic Pd-H complexes have revived far less attention in litterateur than their Pt and Ni counterparts due to the difficulty associated with their preparation and investigation. The complexes are prone to decompose under elimination of hydrogen.[57,58] The studied complexes are frequently stabilised by alkyl-diphosphines and weakly coordinating anions such as $[BF_4]^-$, $[PF_6]^-$, $[CF_3SO_3]^-$ and $[SbF_6]^-$.[50,51,53,58] The acidity of the cationic palladium hydrides was reported to vary with both anion/solvent coordination abillity[53] and electron-donating properties of the ligand.[50] For diphosphines, geometrically distorted complexes provided lower hydride donor ability.[50,57] This was proposed to be an effect of the decrease in LUMO energy that follows a distortion of the square planar geometry towards tetrahedral coordination in complexes of large bite angle ligands.[50,51] The observation by Huang et al.[23] and Murahashi et al.[16] that amide formation was favoured by bidentate phosphines with large natural bite angles, supports this hypothesis. On the other hand, in the present investigation diphosphines were not observed to provide catalytically active complexes. Furthermore, the formation of acidic Pd-H stabilised by aryl phosphines have, to the best of our knowledge not been described in litterateur. In summary, further information concerning the reactivity of acidic Pd-H complexes in aminocarbonylation of amines and olefins is needed, in order to draw qualified conclusions with respect to the viability of the proposed hydride mechanism. Such information could possily, be drawn from competition experiments similar to the experiments contained in Table 1.

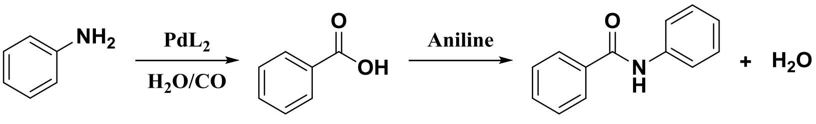
Taking into account that Pd(**L4**)H was reported[59,60] to be unstable and that hydrides, to the best of our knowledge, have not been reported for the applied NHC complexes, a mechanism which do not involve the formation of a hydride species has been considered.



**Scheme 5** Proposed mechanism for the carbonylative formation of benzamide.

According to this hypothesis, the aminocarbonylation of aniline leading to the formation of benzamide go through a Pd(0)-Pd(II) cycle (Scheme 5). Moreover, the high activity of complexes bearing strong σ-donating ligands as well as the formation of carboxylic acid from 2,6-dimethylaniline suggest that first step in this reaction is direct oxidative addition of anilines to a Pd(0) centre and formation of **V** similar as was presented for ruthenium(0) by Kakiuchi et al.[28] and for palladium by Fujiwara et al.[31] Species **2.VI** can undergo further insertion of CO to form **2.VII** which then undergoes nucleophilic attack from aniline to form **2.VIII** under release of ammonia. Notably ammonia release is also observed in primary aniline C-N bond activation by Pd(0) species[12] and by Ru(0) species.[28] Ammonia was detected in the post-reaction gas phase of our experiments. Moreover species **2.VII** can react with water as nucleophile with formation of observed benzoic acid derivatives. Last step in the cycle is reductive elimination of benzamide from species **2.VIII** and regeneration of active species.

As a third proposal which can be mentioned, is the hydroxycarbonylation of aniline for the formation of benzoic acid. Benzoic acid can be formed through one of the previously mentioned mechanisms, followed by condensation of benzoic acid with aniline forming benzamide and water.



**Scheme 6.** Sequential hydroxycarbonylation of aniline and condensation to form benzamide.

Due to the release of water in the condensation reaction, trace amounts of water would be sufficient allow the reaction to proceed by this path. The main arguments for this mechanism are the familiarity of the reaction,[61] the increased reaction rate in "wet" solvent and the observation of benzoic acid in the reaction mixture. The main argument against the hypothesis is the low concentration of acid observed. Applying 2,6-dimethylaniline as the substrate 14% aniline was converted into the corresponding acid which indicate that water was available for this transformation. That the condensation reaction did not proceed in this case, can be associated with the combined steric hindrance of the amine and the acid.[62,63] If the condensation is the hindered step in this reaction pathway a kinetic study should show the accumulation of benzoic acid during the course of the reaction.

In summary, three different reaction mechanisms for the formation of benzamide from aniline has been proposed and the arguments in favouring or disfavouring each of the mechanisms have been discussed.

The role of water in the formation of benzamide from aniline has not been studied to date, but considering the ability of water as a nucleophile it is unlikely that accumulation of benzoic acid would not occur in less active experiments. This has not been observed and therefore this pathway must be disregarded

Considering the proposed hydride mechanism to form benzamide (Scheme 4), cationic palladium hydrides are most frequently applied as water oxidation catalysts.[64,65] Due to the dissimilarity between the organometallic systems which have been reported to form acidic palladium hydride complexes[50,51,53,57,58] and our applied conditions the formation and catalytic activity of this type of complex must be considered unlikely. The formation of amides through oxidative addition of an amine to a Pd(0) complex has previously been proposed in literature.[16,23,26,66,67] This would suggest the proposal to be credible but a thorough mechanistic investigations which would support this theory has not been published. Given the scarcity of publications on both topics further investigation would very likely provide new information on the chemistry of acidic palladium hydrides and palladium driven C-N activation.

## 2.3 **Conclusions**

In summary, novel palladium-based catalytic systems for the synthesis of various substituted N-phenylbenzamides is described. It is noteworthy that the catalytic system is additive free, robust and based on commercially available ligands. The ligands were observed to have a significant influence on the chemoselectivity of the reaction, most likely due to their different ability to stabilise hydride complexes. A wide range of primary anilines including sterically hindered substrates were efficiently converted to benzamides in high yield. Moreover, the possible reaction pathways have been discussed and two catalytic cycle involving the cleavage of (sp$^2$)C-N is proposed.

## 2.4 Experimental

### 2.4.1 General Experimental Details

The chemicals were obtained from Aldrich. Silica gel Geduran® Si 60 (40-63µm) and silica gel 60 F254 TLC sheets were supplied by Merck. Unless mentioned otherwise all reactions were carried out under aerobic conditions with chemicals and solvents used as received from supplier.

### 2.4.2 Characterisation Techniques and Analysis

$^1$H- and $^{13}$C{$^1$H}-NMR spectra were recorded on a Bruker spectrometer respectively at 400 and 100 MHz at 25ºC. Chemical shifts (δ in ppm and coupling constants *J* in Hz) were referenced to residual solvent resonances. GC/MS analyses were performed on an Agilent Technology 6850 Network GC System combined with 5975C VL MSD. ATR-FTIR spectra were recorded on Bruker Alpha-P spectrometer. ESI-MS analysis was performed on a Waters SQD2 equipped with a standard ESI ion source. The basic ESI conditions were: vacuum, $3.7 \cdot 10^{-7}$ mbar; Capillary voltage, 3.0 kV; Dry Heater temperature, 150ºC. Data acquisition and analysis were performed with the MassLynx (version3.0) software package.

### 2.4.3 Synthesis

*1,3-bis-(2,6-diisopropylphenyl)imidazolium chloride (IPrHCl)* was synthesized following a slightly modified procedure published by Nolan et al.[87] 17.5 g (0.1 mol) 2,6-diisopropylaniline was weighted out in a round-bottomed flask and dissolved in 100 mL of EtOH. 7 g (0.05 mol) 40wt% aqueous glyoxal solution was added followed by three drops of formic acid and the mixture left to stirrer at room temperature overnight. The bright yellow precipitate was filtered off, washed with cold methanol and dried on the glass porous filter. Purity was checked by $^1$H. 0.938 g of paraformaldehyde was transferred to a flame dried schlenk under argon and 5.1 mL 4 M HCl in dioxane was added. The mixture was stirred till the paraformaldehyde was completely dissolved and the solution turned clear. 5.037 g bis-imine was added to a flamed dried schlenk under argon, dissolved in 130 mL of THF and cooled to 0ºC. The paraformaldehyde solution was transferred to the bis-imine solution via canula, the mixture was allowed to heat to room temperature and left to stirrer overnight. The white precipitate was filtered off, washed with THF and dried on the glass porous filter. $^1$H NMR chemical shifts corresponded to published data for the 1,3-bis-(2,6-diisopropylphenyl)imidazolium chloride (IPrHCl).[87] $^1$H NMR (401 MHz, $DCCl_3$) δ 9.88(s, 2H, N-CH-N), δ 8.14(d, *J* =1.6, 2H, N-CH-CH-N), δ 7.57 (t, *J* =7.8, 2H, phen-p), δ 7.35 (d, *J* =7.9, 4H, phen-m), δ 2.44(sep, *J* = 6.8, 4H), δ 1.25(dd, *J* =4.9, 6.1, 24H). Overall yield 44%.

*1,3-Bis-(2,6-diisopropylphenyl)imidazolylidene* was synthesized following a slightly modified procedure published by Arduengo et al.[88] 212.5 mg IPrHCl was transferred to a flame dried schlenk, introduced into the glow box and dispersed in 2 mL THF. In the glow box 67.3 mg t-BuOK weight out in a vial, dissolved in 5 mL THF and transferred to the schlenk containing the IPrHCl. The mixture was left to stirrer for half an hour, the schlenk was removed from the glow box and the solvent removed under vacuum. The solid residue was redissolved two timed in hexane and filtered via canula to a separate flame dried schlenk. The solvent was removed under vacuum to yield 127 mg (67%) opalescent white solid. $^1$H NMR chemical shifts corresponded to published data for the 1,3-Bis-(2,6-diisopropylphenyl)imidazolylidene (IPr).[88] $^1$H NMR (401 MHz, THF-$d_8$) δ 8.14(d, *J*=1.6, 2H, N-CH-CH-N), δ 7.57 (t, *J*=7.8, 2H, phen-p), δ 7.35(d, *J*=7.9, 4H, phen-m), δ 2.44(sep, *J*=6.8, 4H), δ 1.25(dd, *J*=4.9, 6.1, 24H).

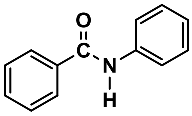
*[$PdCl_2$(IPr)(3-chloropyridine)]* was synthesized following a procedure published by O'Brien et al.[89] 88.5 mg (0.5 mmol) $PdCl_2$, 234 mg (0.55 mmol) IPrHCl, 345.5 mg (2.5 mmol) $K_2CO_3$ and 2 ml (14.8 mmol) 3-chloropyridine was loaded into a schlenk which was heated to 80ºC and left to stirrer overnight. The reaction mixture was cool to room temperature, diluted with $CH_2Cl_2$ and filtered over celite and silica. The solvent was removed under vacuum and the oily solid was washed with pentane to yield 286 mg (89%) light yellow powder. $^1$H NMR chemical shifts of the solid corresponded to published data.[89] $^1$H NMR (399 MHz, $DCCl_3$) δ 8.60(dd, *J*=2.4, 0.5, 1H, N-CH-CCl), δ 8.52(dd, *J*=5.6, 1.4, 1H, N-CH-C), δ 7.55(ddd, *J* =8.2, 2.4, 1.4 , 1H, CCl-CH-C), δ 7.50(t, *J* =2.4, 2H, Ar-p), δ 7.35(d, *J* =7.8, 4H, Ar-p), δ 7.14(s, 2H, N-CH-CH-N), δ 7.07(ddd, *J* =8.2, 5.6, 0.5, 1H, C-CH-C), δ 3.16(sept, *J* =6.8, 2H, me-CH-me), δ 1.48(d, *J* =6.6, 12H, $-CH_3$), δ 1.12(d, *J* =6.9, 12H, $-CH_3$).

*[$PdCl_2(PPh_3)_2$]* was synthesised according to a slightly modified procedure published by Verkuijl et al.[78] In a schlenk flask under argon 176.3 mg (0.56 mmol) [$PdCl_2(CH_3CN)_2$] was dissolved in 40 mL dry dichloromethane and 352.5 mg (1.3 mmol) triphenylphosphine was added. The solution was stirred overnight and the solvent removed under reduced pressure The crude was washed in sequential portions of diethyl ether and ethanol and dried in vacuum overnight. $^1$H NMR and $^{31}$P{$^1$H} NMR chemical shifts of the solid corresponded to published data.[78] $^1$H NMR (401 MHz, $CDCl_3$) δ 7.76-7.65(m, 10H), δ 7.46-7.34(m, 20H). $^{31}$P{$^1$H} NMR (162 MHZ, $CDCl_3$) δ 24.3. Yield 356.1 mg (89%).

### 2.4.3.1 General Procedure for Synthesis of Benzamides

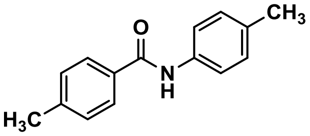
In a 50 mL Parr reactor with Teflon liner, appropriate amounts of palladium catalyst or precursor, phosphine, aniline, mesitylene (internal standard) and 6 ml of THF (HPLC grade from Aldrich) were added. The reaction vessel was closed, purged trice with CO and finally pressurized with CO to required pressure. The reactor was heated to the required temperature and the time was started when the internal reactor temperature reached set temperature. After the reaction, the reactor was cooled to room temperature and depressurized. The reaction mixture was filtered through a short pad of silica and celite before injection in the GC-MS. For product isolation, the reaction mixture was directly absorbed on silica and purified by careful column chromatography using a heptane/ethyl acetate gradient from 0 vol% to 5 vol% ethyl acetate. Evaporation of the solvent yielded the products as white crystalline solids which were analysed by NMR, FTIR and mass spectrometry.

**N-Phenylbenzamide**



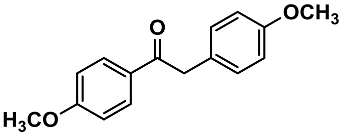
Isolated yield: 93%.$^1$H NMR ($CDCl_3$, δ, ppm): 7.81 (d, *J* = 7.0 Hz, 2H), 7.73 (s, broad, 1H) 7.58 (d, *J* = 8.3 Hz, 2H), 7.53 – 7.47 (m, 1H), 7.43 (t, *J* = 7.3 Hz, 2H), 7.36 – 7.27 (m, 2H), 7.09 (t, *J* = 7.4 Hz, 1H). $^{13}$C NMR ($CDCl_3$, δ, ppm): 165.84, 138.06, 135.17, 132.02, 129.28, 128.98, 127.15, 124.74, 120.31.
GC-MS: m/z (%) = 197.1 [M+] (42), 105.0 (100), 77.0 (45)
IR: 3342, 1653, 1598, 1525, 1437, 1320, 1259, 749, 715, 689
The spectroscopic data was in agreement with literature.[68,69]

### 4-Methyl-N-(4-methylphenyl)benzamide



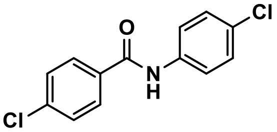
Isolated yield: 77%. $^1$H NMR (CDCl$_3$, δ, ppm): 7.76 (d, *J* = 8.2 Hz, 2H), 7.72 (s, broad, 1H) 7.52 (d, *J* = 8.4 Hz, 2H), 7.28 (d, *J* = 7.9 Hz, 2H), 7.17 (d, *J* = 8.2 Hz, 2H), 2.42 (s, 3), 2.34 (s,1H).
$^{13}$C NMR (CDCl$_3$, δ, ppm): 165.68, 142.41, 135.60, 134.24, 132.36, 129.73, 129.57, 127.13, 120.34, 21.63, 21.04.
GC-MS: m/z (%) = 225.1 [M+] (41), 119.1 (100), 91.1 (30)
IR: 3347, 1646, 1595, 1515, 1402, 1317, 1256, 810, 749.
The spectroscopic data was in agreement with literature.[70,71]

### 4-Methoxy-N-(4-methoxyphenyl)benzamide



Isolated yield: 85%. $^1$H NMR (CDCl$_3$, δ, ppm):7.83 (d, *J* = 8.9 Hz, 2H), 7.65 (s, broad, 1H), 7.52 (d, *J* = 9.0 Hz, 2H), 6.97 (d, *J* = 8.9 Hz, 2H), 6.90 (d, *J* = 9.0 Hz, 2H), 3.87 (s, 3H), 3.81(s, 3H).
$^{13}$C NMR (CDCl$_3$, δ, ppm): 165.26, 162.58, 156.67, 131.31, 128.97, 127.35, 122.22, 114.39, 114.10, 55.66, 55.61.
GC-MS: m/z (%) = 257,1 [M+] (29), 135,0 (100), 77,1 (11).
IR: 3324, 1643, 1605, 1514, 1245, 1029, 823, 527.
The spectroscopic data was in agreement with literature.[72]

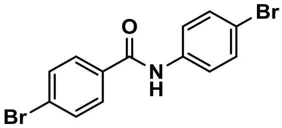
### 4-Chloro-N-(4-chlorophenyl)benzamide



Isolated yield: 72%. $^1$H NMR (CDCl$_3$, δ, ppm):  9.60 (s, 1H), 7.17 (d, *J* = 8.0 Hz, 2H), 6.99 (d, *J* = 8.4 Hz, 2H), 6.80 (d, *J* = 8.0 Hz, 2H), 6.60 (d, *J* = 8.4 Hz, 2H).
$^{13}$C NMR (CDCl$_3$, δ, ppm): 164.49, 137.92, 136.52, 133.34, 129.61, 128.52, 128.47, 127.41, 121.88.

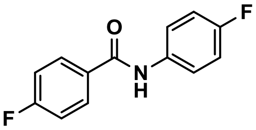
GC-MS: m/z (%) = 265,0 [M+] (24), 139,0 (100), 111,0 (30), 75 (11).
IR: 3343, 1650, 1593, 1515, 1493, 1398, 1315, 1095, 823.
The spectroscopic data was in agreement with literature.[73–75]

### 4-Bromo-N-(4-bromophenyl)benzamide



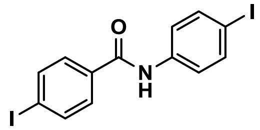
Isolated yield: 67%. $^1$H NMR ($CDCl_3$, $\delta$, ppm): 7.75 (s, broad overlapping, 1H), 7.73 (d, *J* = 8.6 Hz, overlapping, 2H), 7.63 (d, *J* = 8.6 Hz, 2H)., 7.54-7.47 (m, 4H). $^{13}$C NMR ($CDCl_3$, $\delta$, ppm): 164.81, 136.87, 133.57, 132.29, 128.75, 127.03, 121.91, 117.61.
GC-MS: m/z (%) = 354.9 [M+] (28), 182.9 (100), 154.9 (26), 76.0 (15).
IR: 3337, 1649, 1591, 1517, 1393, 1312, 1074, 1010, 820, 753.
The spectroscopic data was in agreement with literature.[76]

### 4-Fluoro-N-(4-fluorophenyl)benzamide



Isolated yield: 84%. $^1$H NMR ($CDCl_3$, $\delta$, ppm): 7.90-7.86(m, 2H), 7.73 (s, broad 1H) 7.60-7.56 (m, 2H), 7.19 (t, *J* = 8.6 Hz, 2H), 7.07 (t, *J* = 8.7 Hz, 2H).
$^{13}$C NMR ($CDCl_3$, $\delta$, ppm): 164.98 (d, $^1J_{C\text{-}F}$ = 252.9 Hz), 164,64 (s) 159.64 (d, $^1J_{C\text{-}F}$ = 244.2 Hz), 133.70 (d, $^4J_{C\text{-}F}$ = 2.9 Hz), 130.88 (d, $^4J_{C\text{-}F}$ = 3.1 Hz), 129.39 (d, $^3J_{C\text{-}F}$ = 9.0 Hz), 122.17 (d, $^3J_{C\text{-}F}$ =7.9 Hz), 116.00 (d, $^2J_{C\text{-}F}$ =11.2 Hz), 115.78 (d, $^2J_{C\text{-}F}$ =11.8 Hz).
GC-MS: m/z (%)= 233.0 [M+] (28), 123.0 (100), 95(37).
IR: 3361, 1650, 1599, 1532, 1503, 1404, 1190, 1095, 830, 759.
The spectroscopic data was not available in literature.

**4-Iodo-N-(4-Iodophenyl)benzamide**



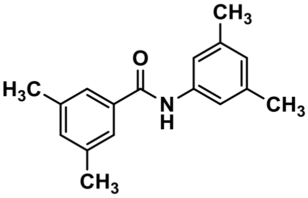
Isolated yield: 52%. $^1$H NMR ($CDCl_3$, δ, ppm): 10.37 (s, 1H), 7.92 (d, *J* = 8.5 Hz, 2H), 7.73 (d, *J* = 8.5 Hz, 2H), 7.69 (d, *J* = 8.8 Hz, 2H), 7.61 (d, *J* = 8.9 Hz, 2H). $^{13}$C NMR ($CDCl_3$, δ, ppm): 165.38, 134.50, 130.08, 122.96, 99.98, 88.02.

ESI-MS: m/z =449.75.

IR: 3326,15, 1649, 1586, 1512, 1390, 1313, 1061, 1006, 817.

The spectroscopic data was in agreement with literature.[77]

**3,5-dimethyl-N-(3,5-dimethylphenyl)benzamide**



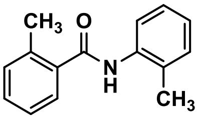
Isolated yield: 82%. $^1$H NMR ($CDCl_3$, δ, ppm): 7.68 (s, broad, 1H), 7.45 (s, 2H), 7.29 (s, 2H), 7.17 (s, 1H), 6.79 (s, 1H), 2.39 (s, 6H), 2.33 (s, 6H). $^{13}$C NMR ($CDCl_3$, δ, ppm): 166.08, 138.93, 138.65, 138.02, 135.34, 133.49, 126.32, 124.85, 117.95, 21.55, 21.43.

GC-MS: m/z (%) = 253.2 [M+] (28), 133,1 (100), 105,1(20), 77,1 (10)

IR: 3264, 2913, 1644, 1598, 1524, 1420, 1318, 1234, 848, 799, 685.

The spectroscopic data was in agreement with literature.[78]

**2-methyl-N-(2-methylphenyl)benzamide**



GC-yield: 80%, $^1$H NMR ($CDCl_3$, δ, ppm): 8.00 (s, broad, 1H), 7.53 (d, *J* = 7.0 Hz, 1H), 7.38 (t, *J* = 7.3 Hz, 1H), 7.30-7.22 (m, 6H), 7.12 (t, *J* = 7.4 Hz, 1H), 2.54 (s, 3H), 2.31 (s, 3H)

$^{13}$C NMR ($CDCl_3$, δ, ppm): 168.08, 136.56, 135.75, 131.36, 130.61, 130.31, 128.99, 126.93, 126.68, 125.98, 125.40, 122.96, 19.94, 17.96.

GC-MS: m/z (%) = 225.1 [M+] (24), 119.1 (100), 91.1 (27), 65.5 (10).
IR: 3262, 1646, 1521, 1493, 1455, 1309.
The spectroscopic data was in agreement with literature.[79]

### 2.4.4 Electron Spray Ionization Mass Spectrometry Experiment

[$PdCl_2$(COD)] (2.1 mg), **L4** (2.9 mg) and aniline (27.9 mg) was placed in a 50 mL Parr reactor fitted with a Teflon liner. 6 ml of THF (HPLC grade from Aldrich) and 8 µL of mesitylene (internal standard) were added. The reaction vessel was closed, flushed trice with CO and pressurized with CO to 50 bar. The reaction mixture was heated to 90ºC and after reaching demanded temperature stirred for an hour. After cooling and depressurization the reaction mixture was divided in two. One part was diluted with THF and injected directly on ESI-MS and the second one was injected to GC-MS for confirmation of aniline conversion.

### 2.4.5 Ammonia Detection Experiment by the Indophenol Blue Method

[PdCl2(COD)] (2.1 mg), **L4** (2.9 mg) and aniline (27.9 mg) was placed in a 50 mL Parr reactor fitted with a Teflon liner. 6 ml of THF (HPLC grade from Aldrich) and 8 µL of mesitylene (internal standard) were added. The reaction vessel was closed, flushed trice with CO and pressurized to 50 bar with CO. The reaction mixture was heated to 90ºC and after reaching demanded temperature stirred for six hours. The Parr reactor was cooled to room temperature and the gas phase was slowly vented to a trap containing 25 ml of distilled water. When no more bubble was observed, water from the trap was transferred to a 50 mL round bottomed flask with stopper and magnetic stirrer bar. The presence of ammonia in solution was observed using a standard colorimetric method.49 The water collected from the trap was added 1 mL 0.01 M ethanolic phenol solution, 1 mL 0.2 mM aqueous sodium nitroprusside solution and 2.5 mL 1% Sodium hypochlorite in 0.4 mL 1 M aqueous NaOH. The flask was sealed with parafilm and stirred for an hour in the absence of light at room temperature. The reaction mixture turned blue in comparison to the blank test with distilled water which remained pale yellow.

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# Chapter 3

# Palladium Catalysed Carbonylation of Anilines in Ionic Liquids

# Palladium Catalysed Carbonylation of Anilines in Ionic Liquids

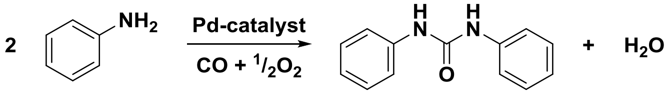
## 3.1 Introduction

Ureas are useful and indispensable compounds commonly included in the structures of a large number of biologically active compounds and are widely used as agrochemicals, dyes, antioxidants, HIV inhibitors, anti-cancer medication[1,2] plasticisers and stabilizers.[3] Furthermore, they are also key intermediates in organic synthesis.[4,5]

Currently, one of the most efficient routes to obtain ureas is via the coupling of an amine with the highly toxic phosgene or its derivatives[6,7] As a result, intense efforts are focused on the development of greener and more sustainable routes for the synthesis of this essential organic compound. In this sense, transition metal-catalyzed carbonylation of amines is considered a powerful alternative method that has attracted steady attention in the past 50 years.[8–12] Among the transition metals, palladium is the most widely used in carbonylation reactions but is usually limited to aromatic amines and both high CO pressure and temperature.[13,14] The search and development of new palladium based systems that could catalyze the carbonylation of aromatic amines and/or aliphatic amines under mild reaction conditions is thus of high interest. Ionic liquids (ILs) have attracted much interest in the last decade due to their inherent properties such as low vapour pressure and toxicity, offering an excellent alternative to volatile organic solvents, making the whole process greener. ILs constitute a special class of compounds that, due to their physical and chemical properties, have a wide field of application catalysis, biomass processing, electrochemistry etc.[15,16] In catalysis, ILs can be used as both reaction media and catalysts and have beneficial effects in many reactions.[17] In addition, ILs can be easily modified with functionalities for a specific catalytic application altering either the cation or the anion.[18] In this sense, ILs were also previously employed in the oxidative carbonylation of amines as reaction media generating biphasic systems by Shi et al., Peng et al. and Mancuso et al.[12,19,20] Furthermore, the use of ILs is reported to be beneficial in many reactions as both reaction media and catalyst.[17,21–24] In this sense, the combination of ILs and new palladium catalysts could lead to an efficient catalytic system for the carbonylation of both aliphatic and aromatic amines under mild reaction conditions as demonstrated by F. Shi et al.[19,25,26] Besides, the use of ionic liquids as reaction media would allow both the separation of the products and the recovery of the precious metal catalyst which is nowadays one of the most important challenges in homogeneous catalysis also in fine chemical industry.

### 3.1.1 Oxidative Carbonylation of Amines

Carbonylation of amines to produce ureas or carbamates have been explored for both aliphatic and aromatic subtrates,[13,27,28] but is most frequently investigated with aniline as a model substrate. In the catalytic carbonylation of amines the nitrogen atom undergoes an oxidation as illustrated in Scheme 1 and therefore it is also known as oxidative carbonylation to distinguish the reaction from the reductive carbonylation of nitroaryls. A large number of transition-metal catalysts such as Mn,[8] Pd,[29] Cu,[30–32] Au,[33,34] Co,[35–37] W,[38] Ni,[39] Rh,[40] and Ru[41] and organo-catalysts such as Se[42–45] and S[46] with either $O_2$/air[12,31,32,34–37,39–41,47–50] or $I_2$[13,38,51,52] as oxidants have been applied in the oxidative carbonylation of amines. The use of $CO/O_2$ mixtures is ideal from a green chemistry point of view as $O_2$ is readily available in atmospheric air and offer almost full atom efficiency in the reaction but it can also problematic due to the explosive nature of $CO/O_2$ mixtures.[53] Work conducted in the explosive range has resulted in very active catalytic systems.[20,48]

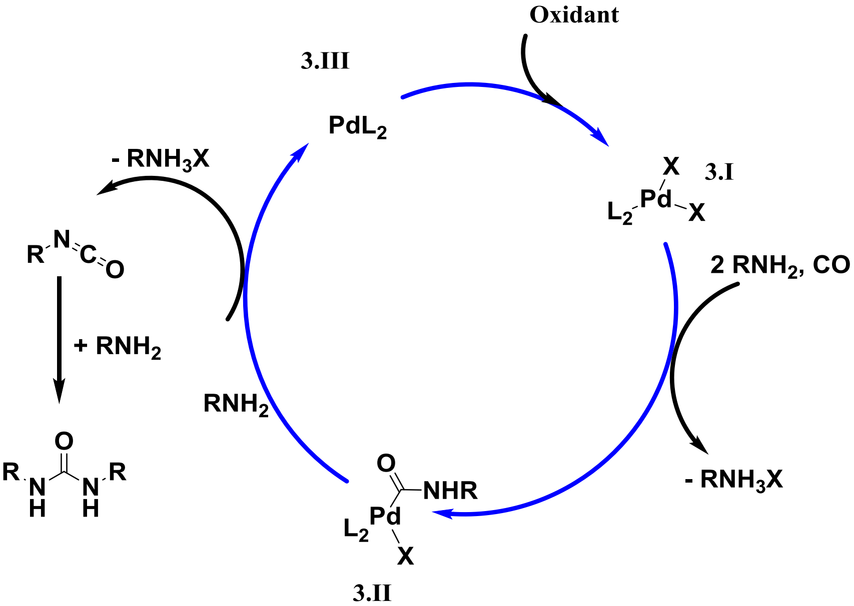


**Scheme 1.** Oxidative carbonylation of aniline.

The mechanism of the palladium-catalysed oxidative carbonylation of amines have been studied by Hiwatari et al.[54]using $I_2$ as oxidant and the authors suggested that the reaction proceeds through a Pd(II)/Pd(0)-cycle via a Pd-carbamoyl intermediate (Scheme 2).

In this mechanism, the active species is a Pd(II) complex that reacts with CO and 2 equivalents of amine to form a Pd-carbamoyl complex and an ammonium salt. Reaction of an amine molecule at the carbonyl of this Pd intermediate then provides the corresponding isocyanate that reacts in situ to form urea as final product.

Hiwatari et al. base their suggestion on the observation that isolated N-propylcarbamoyl-palladium complexes reacted with primary and secondary amines to give N,N-dialkylurea and N,N,N-trialkylurea, respectively while reaction with a tertiary amine produced the free isocyanate. The selectivity of the reaction supports the mechanism as the reaction step **3.II-3.III** can be facilitated by primary, secondary and tertiary amines alike although the intermediate isocyanate can only be formed from a primary amine and the formation of the urea from isocyanate requires a primary or a secondary amine. The repeated observation that N,N,N,N-tertrasubstituded ureas cannot be generated with CO and secondary amines as the only substrates[28,50,55] supports this mechanism.



**Scheme 2.** Mechanism proposed by Hiwatari and co-workers for the Pd-catalysed oxidative carbonylation of primary amines.

A different mechanism must therefore be accredited for the observations published first by Pri-Bar et al.[56] and later by others[57–59] who prepared N,N,N,N-tetrasubstitued ureas in $I_2$-oxidised systems. Giannoccaro et al.[57,60,61] prepared Pd-carbamoyl complexes of both primary and secondary aliphatic amines from various $[PdCl_2(L\text{-}L)]$ precursors and isolated the Pd-complexes along with ammonium chlorides supporting the mechanistic proposal by Hiwatari et al. The Pd-carbamoyl complexes were subsequently oxidized with $Cl_2$, $I_2$ and $CuCl_2$. The oxidation products were found to be more dependent on the amine substitution than the oxidant as secondary carbamoyl halides and primary isocyanates was formed regardless of the halide source. Giannoccaro et al.[60] summarized their observations in a proposed mechanism which is largely in agreement with the proposal made by Hiwatari et al.[54] there is a disagreement on whether or not the ammonium halides re-enter the cycle. The formation of secondary carbamoyl halides would explain the observation of N,N,N,N-tetraalkylureas in reactions where $I_2$ has been used as oxidant.[62] Further support for the mechanisms of Hiwatari et al. and Giannoccaro et al. has been provided by Didgikar et al.[50] and Gabriele et al.[12,28,55,63,64] who both studied the oxidative carbonylation of amines with $Pd(II)/I^-$ catalytic systems using molecular $O_2$ as oxidant and reported a correlation between the nucleophilicity and the reactivity of the substrate for a series of primary arylamines. Comparing aryl- and alkyl-amines Gabriele et al.[28] found primary alkylamines to be more active than arylamines.

Didgikar et al.[50] and Chen et al.[31] have examined the effect of $O_2$ partial pressure as well as total pressure in the oxidative carbonylation of aniline using respectively a palladium and a copper catalyst and found a large influence of the of the $O_2$ partial pressure without affirming the reaction order with respect to $O_2$.

The possible reversibility of oxidative carbonylation is not discussed in litterateur as formation of the carbamoyl (**3.II**) is irreversibly.[54] On the other hand formation of Pd-OMe species is known to be reversible under copolymerization conditions and challenges stabilizing the Pd-carbamoyl complex indicate that the isocyantate elimination is energetically favourable.[60] On the other hand, the reoxidation of the Pd(0)-complex is a likely candidate for a rate determining step. Experiments performed at high $O_2$ partial pressures, and therefore explosive conditions, indicate that the reaction is restrained by the lack of $O_2$ under reaction conditions commonly applied. Experiments performed at very low $O_2$ partial pressures due not lead to a significant drop in activity, suggesting that it is the diffusion of $O_2$ in the reaction media and not the energy barrier of palladium oxidation that inhibits the reaction. To the best of our knowledge no spectroscopic or computational study has detailed the formation of palladium carbamoyl.

In the oxidative carbonylation of amines, ionic liquids (ILs) have been employed as reaction media generating biphasic systems. [12,19,20] In these works, the catalytic systems were constituted by a palladium(II) catalysts, an ionic liquid and in the case of Mancuso et al. an iodide additive such as KI.[12]

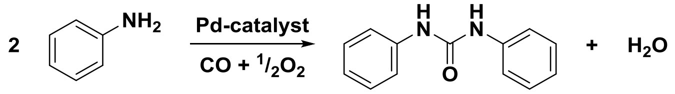
In this chapter the preparation and characterization of palladium-based catalyst/ionic liquid systems for the oxidative carbonylation of aniline into diphenyl urea is described. These catalysts are formed by a palladium (II) precursor, N-donor or P-donor ligands and are evaluated with regard to their catalytic activity, stability and recyclability in the oxidative carbonylation of aniline as a model substrate.

## 3.2 Results and Discussions

### 3.2.1 Influence of Oxidant, Catalyst Loading and Reaction Time

The first part of this work focused on studying the influence of the oxidant on the oxidative carbonylation of aniline to diphenylurea (DPU). $I_2$, $O_2$ and benzoquinone (BQ) were selected as oxidants. BQ has not previously been reported in this reaction although it has been employed in other processes such as Pd-catalyzed olefins carbonylation.[65]

**Table 1.** Influence of the oxidant, catalyst loading and reaction time.



| Entry | Catalyst | Oxidant | Time (h) | TOF ($h^{-1}$) | Conversion (%) | Selectively (%) |
|---|---|---|---|---|---|---|
| 1 | 0.1 | $I_2$ | 4 | 247.5 | 99 | 0* |
| 2[c] | 0.1 | $I_2$ | 4 | 165 | 66 | >99 |
| 3 | 0.1 | $O_2$ | 4 | 197.5 | 79 | >99 |
| 4[d] | 0.1 | BQ | 4 | 220 | 88 | >99 |
| 5 | 0.1 | BQ | 4 | 250 | 100 | >99 |
| 6 | - | BQ | 1 | - | - | >99 |
| 7 | 0.001 | BQ | 1 | 11000 | 11 | >99 |
| 8 | 0.005 | BQ | 1 | 7200 | 36 | >99 |
| 9 | 0.01 | BQ | 1 | 5200 | 52 | >99 |
| 10 | 0.1 | BQ | 1 | 250 | 100 | >99 |
| 11 | 0.01 | BQ | 0.25 | 15600 | 39 | >99 |
| 12 | 0.01 | BQ | 2 | 2350 | 47 | >99 |
| 13 | 0.01 | BQ | 4 | 1100 | 44 | >99 |

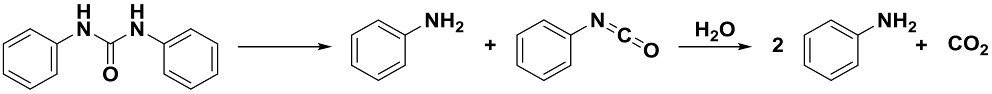
Reaction conditions: Aniline (6 mmol), $[PdCl_2(PPh)_2]$ BQ (6 mmol), $I_2$ (6 mmol), $O_2$ (6 mmol), [BMIM][Cl] (7.5 mmol), mesitylene (0.6 mmol), Toluene (10.5 mL), 140ºC, 10 bar, 1000 rpm. [b]mmol aniline converted/mmol Pd · h. [c]With the addition of $K_2CO_3$ (6 mmol). [d]BQ(3 mmol)

The reaction was initially carried out in a biphasic mixture of toluene and [BMIM][Cl] at 140ºC under 10 bar of CO using 0.1 mol% of $[PdCl_2(PPh)_2]$ as catalyst. The results are displayed in Table 1 (entries 1-5).

After 4 hours of reaction, full conversion was achieved with $I_2$ (entry 1) while only 79% was obtained with $O_2$ (entry 3). The lower conversion in the case of $O_2$ as oxidant was attributed to the poor solubility of the gas in the reaction media.[66,67] Applying BQ in equimolar amount (entry 4) afforded 88% and increasing the amount of BQ to 2 eq. resulted in the full conversion of aniline. Concerning the selectivity, >99% towards urea was reached with BQ and $O_2$ whereas no urea product was obtained when $I_2$ was applied without additional additives. In this latter experiment, only anilinium chloride was obtained. The absence of selectivity towards the urea product with $I_2$ as oxidant can be explained by the insolubility of the anilinium chloride species formed from in-situ generated anilinium iodide[50] and [BMIM][Cl] during the reaction, thus hampering the catalytic performance. Similar results were previously reported when $I_2$ was used as oxidant in the absence of additional base.[61,64] When the reaction was repeated in the presence of 1 eq. of $K_2CO_3$, the selectivity increased up to 66% (entry 2). In view of these results, BQ was selected as oxidant to study the effects of catalyst loading and reaction time on the case reaction.

When the catalyst loading was progressively decreased from 0.1 to 0.001 mol%, a decrease in conversion from 100% to 11% was observed (Table 1, entries 6-9) while the total selectivity towards DPU remained unchanged.

The influence of the reaction time was also studied at 0.01 mol% catalyst (Table 1, entries 8, 10-12). After 1 hour of reaction time, a maximum conversion of 52% was achieved. However, further increase in the reaction time resulted in a decrease in conversion to 47% after 2 hours and to 44% after 4 hours. This result can be explained by the decomposition of diphenylurea into aniline and phenylisocyanate, which further decomposes into aniline and $CO_2$ in the presence of water (**Scheme 3**).[68] The decomposition and reformation of the product also accounts for the need for excess oxidant as noted in entry 4. It is worth pointing out that the studied catalytic system composed by [BMIM][Cl]/Pd/$PPh_3$/BQ is, to the best of our knowledge, among the most active[20,48] in the literature so far with a TOF of 15600 h-1 after 15 minutes reaction (Table 1, entry 9).



**Scheme 3.** Decomposition of DPU into aniline.

Several ligands (Figure 1), namely 1,3-bis(2,6-diisopropylphenyl)-1H-imidazol-3-ium-2-ide **(L1)**, 1,10-phenanthroline **(L2)**, 3-chloropyridine **(L3)**, aniline **(L4)**, benzonitrile **(L5)** and triphenylphosphine **(L6)** were tested in the oxidative carbonylation of aniline. The catalytic experiments were performed with a catalyst loading of 0.01 mol% using the corresponding isolated complexes. Synthetic procedures are described in the experimental section.

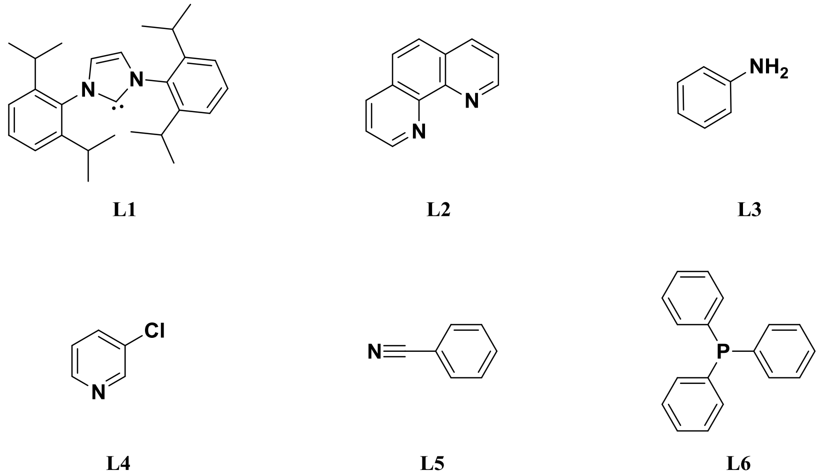


**Figure 1.** Ligands tested in the oxidative carbonylation of aniline.

The results obtained are displayed in Figure 2. The highest conversion (52%) was achieved when the Pd catalysts bearing $PPh_3$ **L6** was used. Similar results in terms of conversion were achieved with the complexes of the monodentate N-donor ligands **L3** and **L5** with conversions of 47% and 44%, respectively. When the mono-carbene complex [$PdCl_2$(**L1**)(**L4**)] and the complex of the bidentate N-donor ligand (**L2**) were tested, similar conversions (26% and 27% respectively) were obtained.

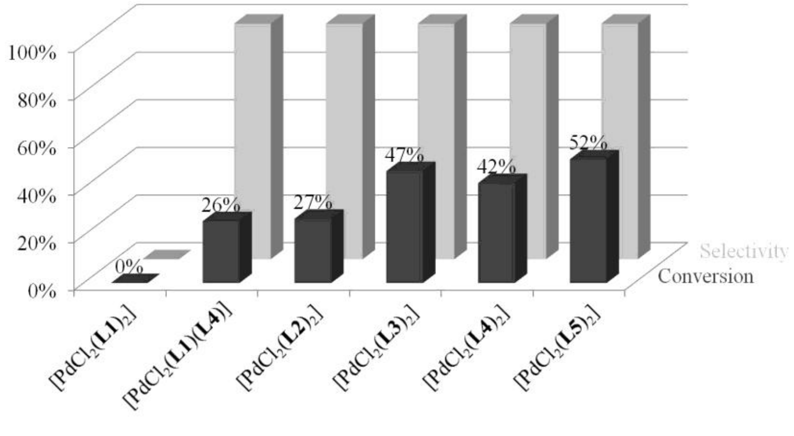


**Figure 2.** Influence of the ligand in the oxidative carbonylation of aniline. Reaction conditions: aniline (6 mmol), Pd-complex (0.01 mol%), BQ (6 mmol), [BMIM][Cl] (7.5 mmol), mesitylene as internal standard (0.6 mmol), toluene (10.5 ml), 140ºC, 60 min., 10 bar CO.

The low conversion obtained with ligand (**L2**) was somehow unexpected, since very good results were obtained by F. Shi et al. although under harsher reaction conditions (175ºC and 50 bar CO).[19]

The use of complex [$PdCl_2$(**L1**)$_2$] bearing two NHC ligands showed no activity, which is in agreement with previous reports.[69,70] Considering the catalytic behaviour reported for bis-Pd(NHC)-complexes an isomerisation from *trans*- to *cis*-comformation is required for addition of the substrate.[69–76] Given the inflexibility of the applied carbene ligands,[77] this isomerisation does not take place thus blocking the coordination of the substrate. The similar results obtained with complexes of **L3** and **L5** are easily explained by the fast displacement of **L5** by **L3** to give in-situ formation of [$PdCl_2$(**L3**)$_2$].

To obtain more insights on the catalytic behaviour of the system based on [$PdCl_2$(**L6**)] as precursor, a high pressure NMR study was performed under in-situ conditions.

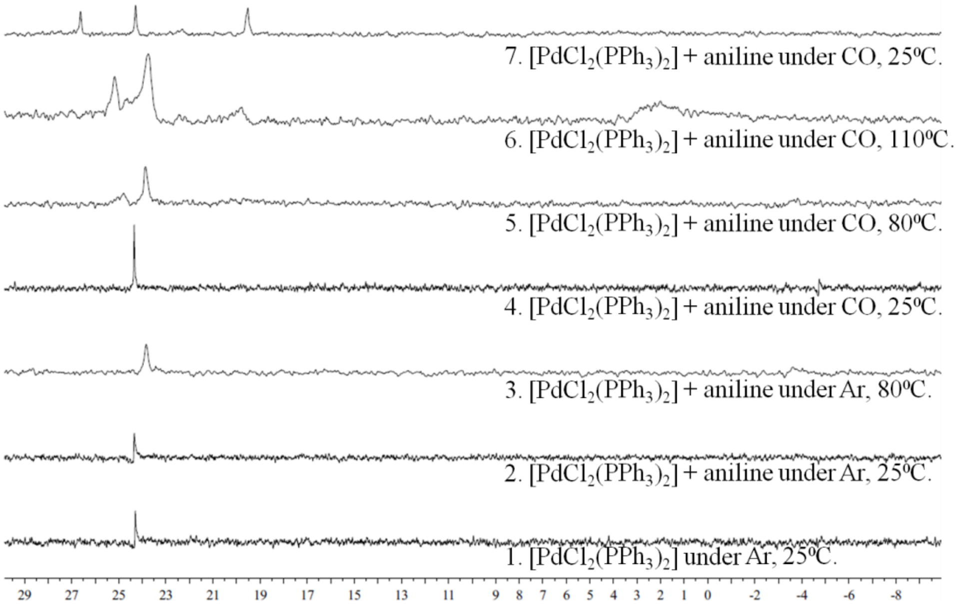


**Figure 3.** In-situ ${}^{31}P$-NMR (sapphire tube, 162 MHz, toluene) of the [$PdCl_2(PPh_3)_2$] catalysed carbonylation of aniline, before, under and after formation of DPU: (1) Initial spectra of the [$PdCl_2(PPh_3)_2$]/[BMIM][Cl] suspension under Ar at 25ºC, (2) after the addition aniline under Ar at 25ºC, (3) the reaction mixture at 80ºC under Ar, (4) the reaction mixture under 5 bar CO at 25ºC, (5) the reaction mixture under CO at 80ºC, (6) the reaction mixture under CO at 110ºC, (7) the reaction under CO at 25ºC.

1. At the start of the experiment, the ${}^{31}P\{{}^{1}H\}$-NMR spectrum (Figure 3, trace 1) displayed one signal at $\delta$ 24.30 ppm corresponding to the ${}^{31}P$ resonance of the [Pd $Cl_2$(**L6**)] precursor.[78]

2. The addition of aniline causes no change in the spectra while heating the mixture under Ar leads to a broadening of the $[PdCl_2(PPh_3)_2]$ signal and an upfield shift to δ 23.86 ppm.
3. No signals belonging to free $PPh_3$ or $OPPh_3$ were observed indicating that the complex was stable under these conditions also under heating.
4. Upon the addition of CO, a signal was immediately observed at δ -4.70 ppm and assigned to free $PPh_3$.[79]
5. Heating the reaction mixture under CO to 80ºC led to the broadening of the signals and the appearance of a new signal at δ 24.82 ppm.
6. Further heating the mixture to 110ºC caused the signals of both free $PPh_3$ and $[PdCl_2(PPh_3)_2]$ to additionally broaden, indicating a rapid exchange between free and coordinated $PPh_3$. Moreover, new signals were observed at δ 25.16 ppm and δ 19.79 ppm.
7. When the sample was cooled to 25ºC, three distinct signals at δ 26.64 ppm, δ 24.30 ppm and δ 19.54 ppm were observed. The signal at δ 24.30 ppm was readily assigned to $[PdCl_2(PPh_3)_2]$.[78,79] The multiplicity and chemical shifts of the two other signals could match those of $Pd(CO)n(PPh_3)_x$, and $[PdCl(CONHPh)(PPh_3)_2]$.[54]

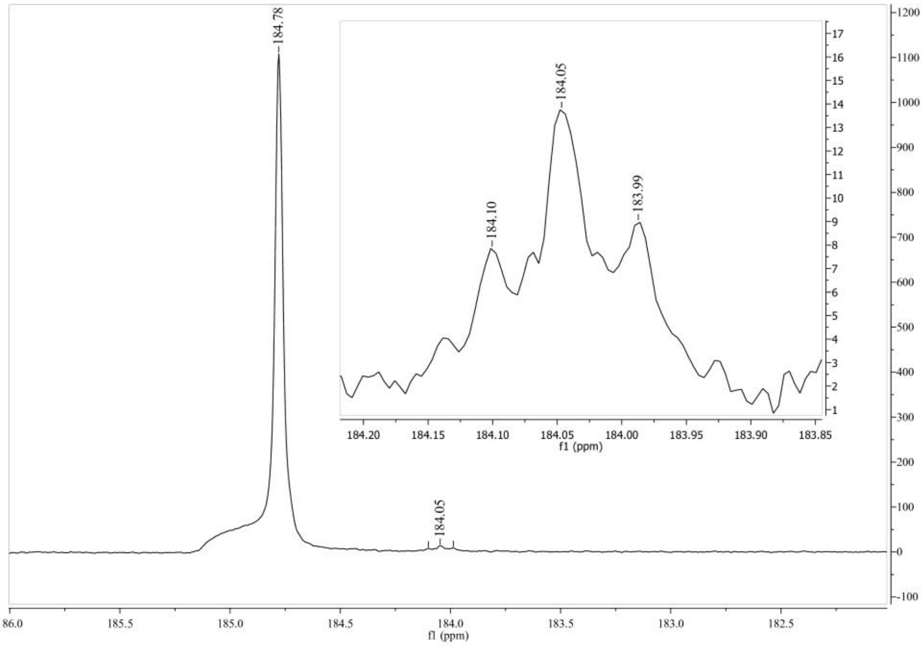


**Figure 4.** *In-situ* $^{13}C\{^1H\}$-NMR (sapphire tube, 100 MHz, toluene, 25ºC, 5 bar $^{12}CO$:$^{13}CO$ = 3:2) of the $[PdCl_2(PPh_3)_2]$ catalysed carbonylation of aniline after the formation of DPU.

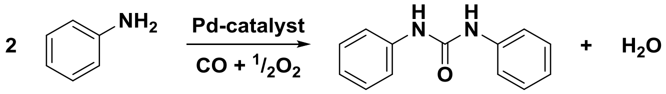
Before, under and after the HP-NMR experiment $^{13}C\{^1H\}$-spectra were recorded. The area between δ 186 ppm and δ 182 ppm of the spectrum recorded at the end

of the experiment at room temperature is displayed in Figure 4. It features the free CO at δ 184.78 ppm with a shoulder at app. δ 185 ppm as the most dominant peak and a triplet at δ 184.05 ppm. This latter signal was assigned to the Pd-carbamoyl complex [PdCl(CONHPh)$(PPh_3)_2$] based on literature values.[54] The shoulder at δ 185 ppm was suggested to arise from complexes of the general type of Pd(CO)n$(PPh_3)_x$ although such signals should also display multiplicity. The intensity of the CO peak and overlapping signals, caused the possible Pd(CO)n$(PPh_3)_x$ peak to be to poorly resolved for any multiplicity to be observed.
The stability and reactivity of [$PdCl_2(PPh_3)_2$] correlates well with the results obtained during catalytic testing. As $PPh_3$ do not interchange with aniline even at elevated temperatures, the improved conversion obtained with [$PdCl_2(PPh_3)_2$] as catalyst is directly related to the coordination of $PPh_3$. Under an atmosphere of CO and with heating to 110ºC, [$PdCl_2(PPh_3)_2$] underwent a rapid exchange of $PPh_3$ and CO at the metal center which activated the complex for the formation of the Pd-carbamoyls intermediate proposed by Hiwatari et al.[54] and Giannocarro et al.[60] To the best of our knowledge it is the first time the palladium-carbamoyl complex has been observed under in-situ conditions.

### 3.2.2 $O_2$ as Oxidant in the Oxidative Carbonylation of Aniline to Diphenylurea

Initial results, using $O_2$ as an oxidant, indicated that the low solubility of $O^2$ caused the incomplete conversion of the substrate (Table 1, Entry 3). Therefore, it was decided to study the influence of the stirring rate in the oxidative carbonylation of aniline to diphenylurea using $O_2$ as oxidant since the solubility of $O_2$ into the ionic liquid could be partially overcome by optimizing the stirring rate.

**Table 2.** Influence of the stirring rate, catalyst loading, IL amount and pressure.[a]



| Entry | Catalyst (mol%) | Pressure (bar) | Stirring (rpm) | TOF ($h^{-1}$) | Conversion (%) | Selectivity[b] (%) |
|---|---|---|---|---|---|---|
| 1 | 0.1 | 10 | 500 | 102.5 | 41 | >99 |
| 2 | 0.1 | 10 | 1000 | 197.4 | 79 | >99 |
| 3 | 0.1 | 10 | 1400 | 195 | 88 | >99 |
| 4 | - | 10 | 1000 | - | 0 | n.d. |
| 5 | 0.01 | 10 | 1000 | 1900 | 76 | >99 |
| 6 | 0.02 | 10 | 1000 | 198 | 79 | >99 |
| 7 | 0.5 | 10 | 1000 | 97.5 | 78 | >99 |
| 8 | 1 | 10 | 1000 | 39.5 | 79 | >99 |
| 9 | 10 | 10 | 1000 | 17.5 | 70 | >99 |
| 10 | 0.1 | 10 | 1000 | 2.1 | 82 | >99 |
| 11 | 0.1 | 5 | 1000 | 137.5 | 55 | >99 |
| 12 | 0.1 | 20 | 1000 | 200 | 80 | >99 |
| 13 | 0.1 | 30 | 1000 | 207.5 | 83 | >99 |
| 14[c] | 0.1 | 10 | 1000 | 215 | 86 | >99 |
| 15[d] | 0.1 | 10 | 1000 | 250 | 100 | >99 |
| 16[e] | 0.1 | 10 | 1000 | 5 | 2 | >99 |
| 17[f] | 0.1 | 10 | 1000 | 68 | 27 | >99 |

[a]Reaction conditions: aniline (6 mmol), [$PdCl_2(PPh)_2$], $O_2$ (6 mmol), [BMIM][Cl] (7.5 mmol), mesitylene (0.6 mmol), Toluene (10.5 mL), 140ºC, 4h., 1000 rpm. [b]mmol aniline converted/mmol Pd h. [c][BMIM][Cl] (15 mmol). [d][BMIM][Cl] (30 mmol).[e]No [BMIM][Cl]. [f] DPU(2.4 mmol), aniline (12 mmol), [$PdCl_2(PPh)_2$], O2 (12 mmol), [BMIM][Cl] (13 mmol), mesitylene ( 1.2 mmol), Toluene (21 ml), 140ºC, 1h. n.d.=not determined.}

The results are shown in Table 2 (entries1-3) and an increase in conversion from 41% to 79% was observed when the stirring rate was increased from 500 to 1000 rpm but further increase in the stirring rate to 1400 rpm did not show any improvement in conversion. This fact confirms that using $O_2$ as oxidant the mass transfer is rate limiting when a stirring rate below 1000 rpm is used.

Next, the catalyst loading was optimized (Table 2, entries 4-10) between 0.01 and 10 mol% (Table 2, entries 5-10). The results show that there is no influence of catalyst loading on conversion when $O_2$ was used as oxidant, which is in contrast with the results obtained with BQ (Table 2, entries 4-8). Therefore, it appears that the oxidative carbonylation of aniline under our reaction conditions is not first order with respect to the catalyst using $O_2$ as oxidant. The catalytic performance with total pressure was also investigated under our reaction conditions using total pressures of 5, 10, 20 and 30 bar (Table 2, entries 6, 11-13). An increase in conversion from 55% to 79% was observed when total pressure was increased from 5 to 10 bar respectively. Further increase in total pressure to 20 or 30 bar did not show any improvement in terms of conversion Table 2, entries 12, 13). In entries 6, 14-16 (Table 2), the results concerning the influence of the IL amount in the investigated reaction are depicted. The highest IL amount resulted in the highest conversion without affecting the selectivity. The conversion increases up to 100% when 30 mmols of the IL are employed.

The strong influence of the IL on the reaction, indicate an interaction between the IL and either the substrate, the catalyst or the product. The formation of Pd-NHC complexes form palladium precursors in imidazolium IL has been reported previously but given the negative effect on the reaction obtained when applying NHC-complexes (Table 2, entries 1-2) the in-situ formation of a Pd-NHC complex has to be disregarded in the case of the applied reaction conditions. An experiment started at a point close to full conversion (Table 2, entry 17) lead to the conversion of only 27% of the added aniline, indicating a negative effect of high substrate concentrations on the reaction. This led to examination of the influence of the nature of the IL.

### 3.2.3 Influence of Ionic Liquids Ions in the Oxidative Carbonylation of Aniline to Diphenylurea with $O_2$ as Oxidizing Agent

Physical and chemical properties of ionic liquids can be tuned up by selecting the appropriate cation or anion, which in turn will influence the catalytic performance for a studied reaction.

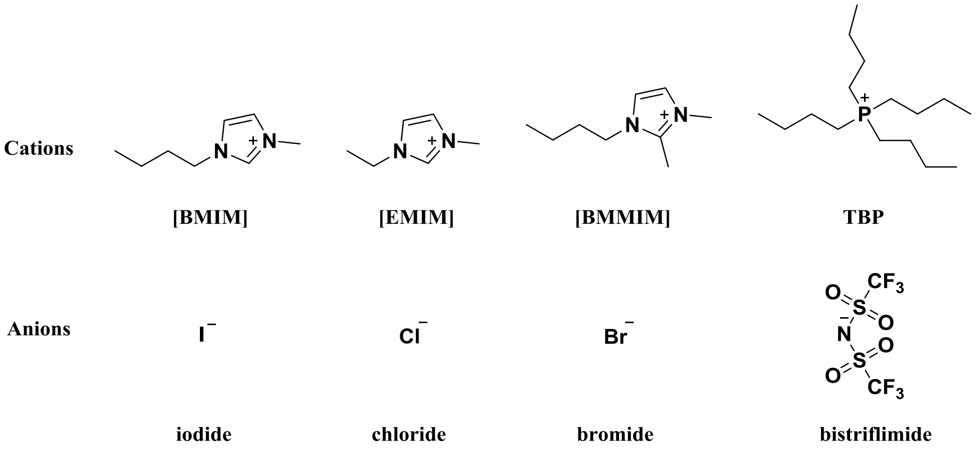


**Figure 5.** Cations and ions employed in this study.

Here, various ions were tested in the oxidative carbonylation of aniline to diphenylurea under our reaction conditions as shown in Figure 5.

1-btyl-3-methylimidizalium ([BMIM]) was selected as the starting cation and was tested with different anions, namely, iodide, bistriflimide, bromide and chloride (Figure 6). The best results in terms of conversion were obtained with [BMIM][Br] ionic liquid with up to 88% conversion. [BMIM][Cl] provided 76% conversion and [BMIM][$(CF_3SO_2)_2N$] 57%. On the other hand, [BMIM][I] inhibited completely the catalytic activity, which was unexpected since both

Gabriele et al. and Peng et al. described that iodide could play a key role in the catalytic reaction.[20,80] Didgikar et al.[50] optimized the I-/Pd-ratio and obtained the highest conversion with 5 eq. of iodide promoter with respect to palladium while both higher and lower I$^-$/Pd-ratios resulted in lower conversion. The application of [BMIM][I] give a I$^-$/Pd-ratio > 1000 and it is therefore plausible that the high concentration of iodide poisons the catalyst. The effect of the alkyl on the cation was studied comparing the results obtained with [BMIM][Cl] and with [EMIM][Cl]. However, no differences in conversion were observed by varying the length of the alkyl chain in 1 position of the imidazolium moiety. The use of other cations such as [BMMIM]$^+$ or [TBP]$^+$ in the ionic liquid did not result in any activity. Among the anions, Br$^-$ gave the best results but [(CF$_3$SO$_2$)$_2$N] rendered an spontaneous separation of DPU and consequently [BMIM][(CF$_3$SO$_2$)$_2$N] ionic liquid was selected to carried out the recycling experiments.

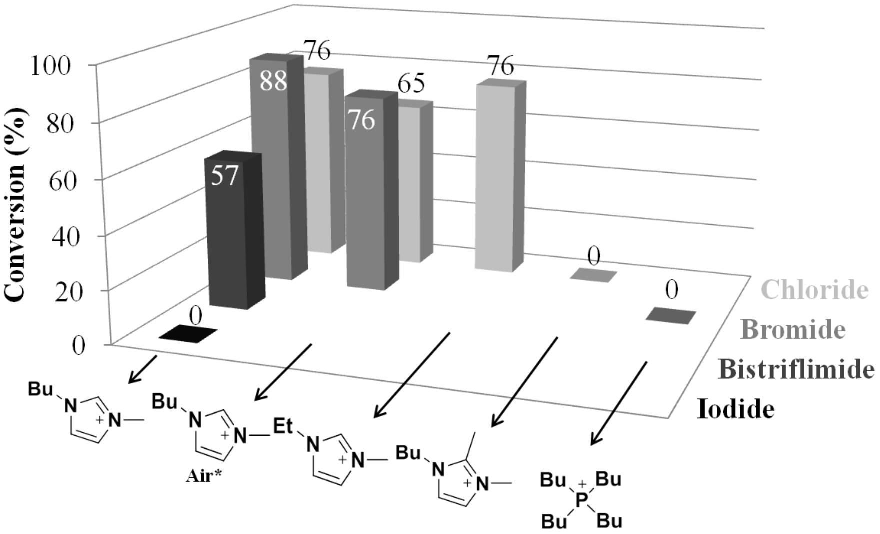


**Figure 6.** Effect of the ionic liquid ions. Reaction conditions: aniline (12 mmol), 10 bar (CO/O$_2$ = 9/1), [PdCl$_2$(PPh)$_2$] (0.1 mol\%), IL (15 mmol), Toluene (21 mL); mesitylene (1.2 mmol), 140ºC, 500 rpm, 60 min, DPU as sole product. *10 bar (CO/Air = 3/1).

However, when the catalytic system was recycled, a decrease in conversion was clearly observed from 57% (first cycle) to 19% (second cycle and to 10% in the third run.

The strong influence of the cat-ion structure on the oxidative carbonylation of aniline and the absence of a proton in the C$_2$-position effectively quenching the reaction can be explained by the increased solubility of the weakly basic aniline in a acidic imidazolium IL.[81] The acidity of the imidazolium ILs is affected by the alkyl-chain length and the ionic interaction[82,83] making [BMIM][(CF$_3$SO$_2$)$_2$N] the more acidic and thus better solvent for aniline[84,85] but the IL-anion must also be expected to enter into palladium coordination sphere where the less coordinating $[(CF_3SO_2)_2N]^-$ fail to stabilize the catalyst sufficiently making [BMIM][Br] the best compromise between solvation strength and coordination ability.

## 3.3 Conclusions

Selective oxidative carbonylation of aniline to diphenylurea was carried out in the presence of a catalytic system comprising of $[PdCl_2(PPh_3)_2]$ as catalyst and [BMIM][Cl] with a TOF of 15600 $h^{-1}$ and 1900 $h^{-1}$ when benzoquinone or $O_2$ were used as oxidants respectively. The TOF achieved with benzoquinone as oxidant was, to the best of our knowledge, the highest reported so far in mild reaction conditions (140ºC and 10 bar). In order to investigate the influence of the ionic liquids several cations and anions were applied, the best results were achieved with [BMIM][Br] while the employment of $[BMIM][(CF_3SO_2)_2N]$ drove a spontaneous product separation. Unfortunately recycling experiments were not as good as expected and the catalytic system could be reused three times but with loss of activity from the first reuse. The unexpected recycling results are attributed to lack of stability of the palladium catalytic species during work-up of the reaction.

## 3.4 Experimental

### 3.4.1 General

Solvents were supplied by Panrec. Deuterated solvents where supplied by Oxford Isotopes. Solvents for synthesis of ILs or complexes were dried using a MBraun MB-SPS-800 solvent purification system or distilled by standard techniques (acetonitrile and ethyl acetate from $CaH_2$ and THF from Na/benzophenone). Chemicals were supplied by Sigma-Aldrich. For the catalytic tests reagents were used as supplied and manipulation was conducted under atmospheric conditions. ILs was purchased from Sigma-Aldrich or synthesized inhouse. Prior to use they were dried under vacuum at 70ºC for more than 24 hours. Complex synthesis was performed under argon using schlenk techniques or in a dry nitrogen glow box when necessary.

### 3.4.2 Characterization Techniques and Analysis

NMR analysis was performed using Varian or Oxford 400 MHz instruments. $^1H$ NMR and $^{13}C\{^1H\}$ NMR spectra were referenced with respect to the residual solvent peak as published by Fulmer et al.[86] $^1H$ NMR (400 MHz DMSO) $\delta$ 2.5(p, $J$ = 3.7, 1.8) $^{13}C\{^1H\}$ NMR (100 MHz DMSO) $\delta$ 39.52. $^{31}P\{^1H\}$-NMR was referenced with respect to $H_3PO_4$. The Fourier transform was analysed using MestReNova 6.0.2.

GC-MS was performed using an Agilent 220-MS fitted with a HP-5, 30 m x 250 µm x 0.25 µm column.

Samples were taken from the solvent and IL phases and analysed by respectively GC-MS and $^1$H NMR. Residual aniline concentration was quantified using the internal standard method, mesitylene was chosen as internal standard. $^1$H NMR was performed in DMSO-$d_6$ using and spectra were collected with a relaxation time of 2 x T1. DPU concentration and residual aniline was quantified using the internal standard method with [BMIM][Cl] as internal standard and the regression analysis shown in the appendix. IL-phases from selected experiments were extracted using 50 mL water and 2 x 50 mL diethyl ether. The diethyl ether extractions was combined and dried with $MgSO_4$ and the solvent removed at reduced pressure to obtain a dark brown solid. The water extraction was dried to a viscous liquid at reduced pressure. Both was analysed by $^1$H NMR in DMSO-$d_6$ and confirmed to contain DPU from the ether extraction and $[BMIM]^+$ from the water extraction. Residual aniline was found in both water and ether extractions. Crude DPU from the diethyl ether extraction was further purified by column chromatography using 60 Å silica and a hexane:EtOAc gradient from 9:1 to 6:4 yielding light brown needle shaped crystals.

## 3.4.3 Synthesis

*[PdCl$_2$(IPr)$_2$]* was synthesized using standard glowbox and schlenk technique. 29 mg $PdCl_2$ was transferred to a flame dried schlenk and introduced into the glowebox. $PdCl_2$ was suspended in 5 mL THF. 127 mg IPr was weighted into a vial and dissolved in THF before it was transferred to the $PdCl_2$ suspension. THF was added to a total volume of 25 mL and immediately a discoloration of suspension from dark brown to hazy yellow was observed. The mixture was allowed to stir overnight and the solvent was removed under vacuum. The remaining solid was purified by column chromatography over silica with 1:1 hexane/$CH_2Cl_2$ to yield 41 mg (54%) light yellow solid. $^1$H NMR chemical shifts of the solid corresponded to published data.[70] $^1$H NMR (401 MHz, $DCCl_3$)

δ 7.35(t, *J*=14.0, 4H, Ar-p), δ 7.07(d, *J*=7.6, 8H, Ar-m), δ 6.72(s, 4H, N-CH-CH-N), δ 2.88(sept, *J*=7.6, 8H, me-CH-me), δ 0.90(t, *J*=7.6, 24H, -$CH_3$.

*[PdCl$_2$(NH$_2$Ph)$_2$]* was synthesised according to a slightly modified procedure published by Chaudhari et al.[40] 118.5 mg (0.67 mmol) $PdCl_2$ was suspended in 9 mL benzene and 1 g (11 mmol) aniline was added. The mixture was refluxed for two hours during which a warm yellow precipitated formed. The precipitate was filtered of and recrystalised from DMF and pentane to yield 191 mg (79%) pure yellow solid.

*[PdCl$_2$(Phen)]* was synthesised by a slightly modified procedure from A. Bontempi et al.[87] To a schlenck flask 64.9 mg (0.25 mmol) of [$PdCl_2(CH_3CN)_2$] and 10 mL of dichloromethane was added and stirred to complete solution. Addition of 45.1 mg (0.25 mmol) of 1,10-phenantroline caused immediate precipitation. The precipitate was filtered of, washed in dichloromethane and dried

in vacuum. $^1$H NMR chemical shifts of the solid corresponded to published data.[88] $^1$H NMR (401 MHz, DMSO-$d_6$) δ 9.35(d, *J* =5.4, 2H), δ 8.14(d, *J* =8.2, 2H), δ 9.98(d, *J* =8.2, 2H), δ 8.29(s, 2H).

*IPr*, *[PdCl$_2$(IPr)(3-chloropyridine)]* and *[PdCl$_2$(PPh$_3$)$_2$]* was prepared as described in chapter 2.

*1-Butyl-3-Methylimidazolium Chloride ([BMIM][Cl])* was synthesized according to a procedure published by J. Dupont et al.[89] 100 mL MeCN was charged to a flame dried schlenk under argon followed by 78.2 mL (0.5 mol) 1-methylimidazol and 97.9 mL 1-chlorobutane. The flask was fitted with a condenser and brought to a gentle reflux. After 48 hours, the reaction was allowed to cool to room temperature and the progress controlled by TLC. The reaction was reheated and allowed to reflux for another 36 hours. The completion of the reaction was confirmed by TLC. The reaction mixture was transferred by canula to a well stirred schlenk containing 500 mL of EtOAc and a seeding crystal. The flask was cooled to -30ºC for two hours, the solvent mixture was removed by canula filtration and the solid dried under vacuum to give yield 161.5 g (99%) of 1-Butyl-3-Methylimidazolium Chloride. $^1$H NMR chemical shifts of the solid corresponded to published data.[90] $^1$H NMR (401 MHz, $DCCl_3$)
δ 10.8(s, 1H, N-CH-N), δ 7.22(d, *J* =14.0, 2H, N-CH-CH-N), δ 4.32(t, *J* =7.6, 2H, N-$CH_2$-C), δ 4.12(s, 3H, N-$CH_3$), δ 1.91(d, *J* =7.6, 2H, C-$CH_2$-C), δ 1.38(t, *J* =7.6, 2H, C-$CH_2$-me), δ 0.97(t, *J* =7.4 3H, C-CH3).

*1-Butyl-3-Methylimidazolium Bromide ([BMIM][Br])* was synthesized according to the procedure described for [BMIM][Br]. $^1$H NMR chemical shifts of the solid corresponded to published data.[91]
$^1$H NMR (400 MHz, dmso-$d_6$)
δ 9.72(s, 1H, N-CH-N), δ 7.94(d, *J* =14.0, 2H, N-CH-CH-N), δ 4.21(t, *J* =7.6, 2H, N-$CH_2$-C), δ 3.89(s, 3H, N-$CH_3$), δ 1.73(d, *J* =7.6, 2H, C-$CH_2$-C), δ 1.19(t, *J* =7.6, 2H, C-$CH_2$-me), δ 0.83(t, *J* =7.4 3H, C-$CH_3$).

### 3.4.4 Catalytic test

The catalytic tests were performed in two different reactors: A 300 mL Parr autoclave and a 100 mL Berghof autoclave. The procedure for each reaction is described below.

Test of reaction conditions were performed in a 100 mL magnetically stirred Berghof autoclave fitted with a Teflon liner. The reactor was equipped with thermocouple, manometer, hotplate and heating block where the thermocouple and hotplate was connected to a Berghof control unit. For each experimental run the reactor was loaded with catalyst, IL, internal standard, substrate and solvent, flushed trice with app. 1 bar CO before it was charged with 9:1 CO/$O_2$ mixture unless otherwise stated. Temperature was set from the control unit and stirring rate from the hotplate.

In an typical run the autoclave was loaded with 1.2 g [BMIM][Cl], 4.0 mg [PdCl$_2$(PPh$_3$)], 10.5 mL Toluene, 0.55 mL aniline, 84 µL mesitylene, 9 bar CO and 1 bar $O_2$ and heated to 140ºC under stirring at 1000 rpm.

For all experimental runs the liquid volume of the reactor was kept at 12.4 mL. The heating block was preheated to 150ºC before the charged reactor was inserted and the time to reach set temperature was 30 min. Temperature deviations from the set temperature were within ± 3ºC. Reaction time was counted form the onset of set temperature. At the end of the experimental run the heating block was removed and the reactor was cooled to room temperature with ice. At room temperature the pressure was released and the solvent phase and the IL phases were separated. For the recycling test the IL phase was extracted as described below and the dried IL was reused.

Test of reaction conditions were performed in a 300 mL mechanically stirred Parr autoclave fitted with a Teflon liner. The reactor was equipped with thermocouple, manometer, heating mantle and pressure transmitter. Thermocouple, heating mantle and pressure transmitter were connected to a Parr control unit which controlled temperature, pressure and agitation. For each experimental run the reactor was loaded with catalyst, IL, internal standard, substrate and solvent, flushed trice with app. 1 bar CO before it was charged with 9:1 $CO/O_2$ mixture unless otherwise stated. In an typical run the autoclave was loaded with 2.4 g [BMIM][Cl], 8.0 mg $[PdCl_2(PPh_3)]$, 21 mL Toluene, 1.1 mL aniline, 168 µL mesitylene, 9 bar CO and 1 bar $O_2$ and heated to 140ºC under stirring at 500 rpm.

For all experimental runs the liquid volume of the reactor was kept at 24.7 mL and the time to reach set temperature was 30 min. Temperature deviations from the set temperature were within ± 3ºC. Reaction time was counted form the onset of set temperature. At the end of the experimental run the heating mantle was removed and the reactor was cooled to room temperature with ice. At room temperature the pressure was released and the solvent phase and the IL phases were separated.

### 3.4.5 HP-NMR

0.436 mmol of [BMIM][Cl] was dissolved in 0.5 mL of methanol and transferred to the tube which was placed under vacuum overnight. To the tube was added 22 µmol $[PdCl_2(PPh_3)]$, 0.2 mmol Aniline, 0.8 mL toluene-$d_8$ and 5 bar $^{12}CO$:$^{13}CO$ = 3:2 in 5 mm sapphire tube.[92] Prior to the addition of CO the content of the tube was kept under Argon using schlenk technique. Spectra were recorded with a 400 MHz Variant spectrometer. $^{13}C\{^1H\}$ and $^1H$ spectra were referenced to the residual solvent signal in accordance with literature[86] while $^{31}P\{^1H\}$ was referenced with respect to $H_3PO_4$. If not stated otherwise the spectra were collected at room temperature.

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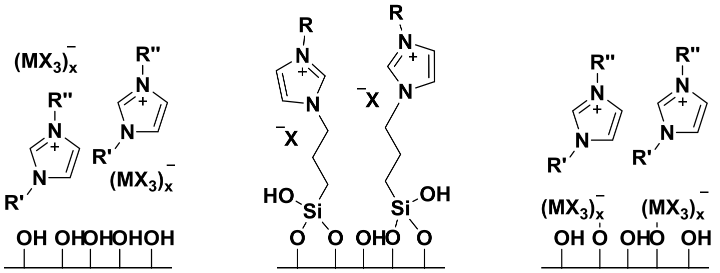
# Chapter 4

# Oxidative Carbonylation of Aniline in Continuous Flow

# Oxidative Carbonylation of Aniline in Continuous Flow

## 4.1 Organically Modified Silicas

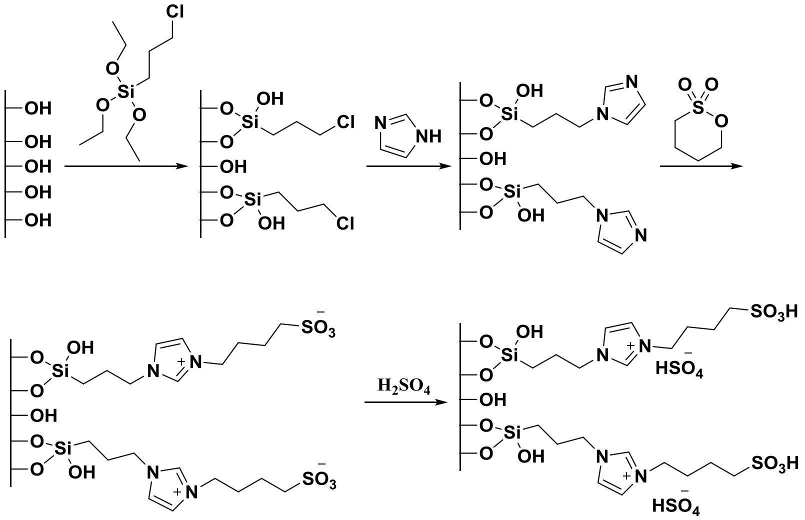
Continuous flow reactions in IL and over SILP catalysts were introduced in chapter 1. As described, challenges concerning catalyst stability have been observed by several groups as well as unexpected catalyst-support interactions.[1] The interest in the application of IL's in continuous reactions have given interest to the anchoring of IL's to solid supports.[2,3] This can proceed through non-covalent interactions (hydrogen bonding, capillary forces and van der Walls interaction) (i, Figure 1),[4–6] or covalent bonding of either the cation or the anion of the IL (ii-iii, Figure 1).[7] The non-covalently anchored IL phase represent the classical SILP while solids functionalised with charged fragments are described with labels such as cSILP or SILP.



i. Supported liquid phase.
ii. Anchoring by the cation.
iii. Anchoring by the anion.

**Figure 1** Immobilizing ionic liquids.

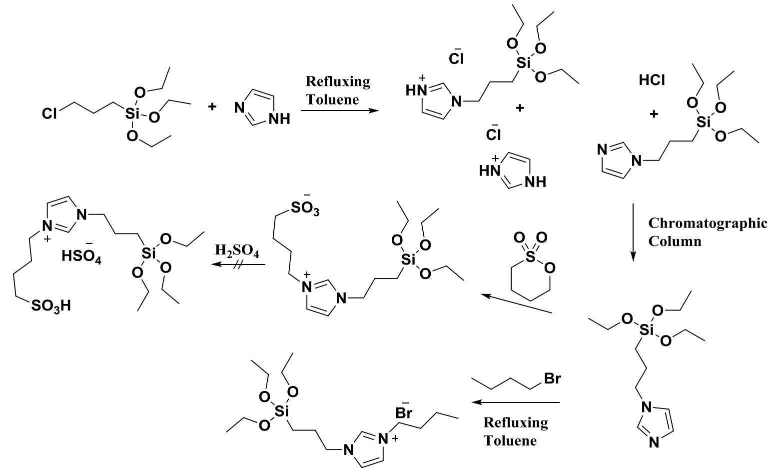
For silica the covalent functionalisation of a solid support with an IL proceed either through the bottom-up (Scheme 1), top-down approach (Scheme 2) or through synthesis of organosilicas by co-condensation.[8–12] Within the bottom-up approach reported methods[13–17] show little variation while the top-down approach is reported via three general procedures: Neat without base,[18–20] in solvent without base[21–24] and in solvent with base.[25] The approach must be chosen on basis of the stability of the alkoxysilane, as the hydrolysis of the silane can hinder the anchoring of the organic fragment at a later stage of the top-down synthesis. The bottom-up synthesis is, on the other hand, challenged by the multistep functionalisation of the silica surface. In this work the bottom-up approach and the top-down approach without base have been applied.



**Scheme 1.** Bottom-up synthesis of IL-functionalised silica.

Functionalised silicas have been used as independent catalysts in cases of the functionalisation being an organocatalyst[17,26–28] or when the functionalisation has been the ligand of a transition-metal centre.[22,29–34] Funtionalised silicas have also been applied as supports for transition metal nano-particles.[15,35–37] Examples of organocatalysts tethered to solid support are seen in the intramolecular aldol reaction,[25,38] alcohol oxidation,[39] condensation reactions,[10,23,40] Baeyer–Villiger reaction,[18] Michael addition[41] and the synthesis of cyclic carbonates from $CO_2$.[8,20,26,27] The first heterogenization of a homogeneous metal catalyst through the tethering to a solid was performed by Valkenberg et al. anchoring [$AlCl_4^-$] to silica[7] applying (ii) and (iii) (Figure 1) and their approach has since found frequent application.[2,42,43]

Bulk ionic liquids do not preserve all of their previously mentioned physio-chemical properties (see chapter 1) when tethered to a solid. Molecular mobility and self-organization, which are key characteristics of IL's, are lost as well as their solvation strength, conductivity and viscosity.[43]



**Scheme 2.** Top-down synthesis of IL-functionalised silica.

On the other hand, the physio-chemical properties of the ILs are conserved when they are immobilized by non-bonding interaction (see chapter 1) in the form of a SILP material. In the most commonly applied form of a SILP catalyst the IL is anchored strictly to a inorganic support[44] but the anchoring of IL's to functionalised supports is also known and this form of hybrid SILP with enhanced interaction between the support through the functionalisation and the IL-film have previously been applied in hydroformylation,[45,46] Suzuki–Miyaura[47] and Mizoroki–Heck.[48]

In this work a SILP prepared on functionalised silica through the deposition of a palladium complex dissolved in a BMIM-IL has been applied to the oxidative carbonylation of aniline yielding diphenyl urea. The oxidative carbonylation of aniline has been investigated as a model reaction for the formation of substituted ureas. Ureas are important intermediates in organic synthesis of pharmaceuticals,[49–51] agrochemicals,[52,53] plasticizes,[54,55] dyes[56,57] and antioxidants.[58] Compared to the biphasic approach described in chapter 3, the amount of IL applied is reduced greatly. Even though the IL was found to have a direct and significant positive influence on the reaction the application of such conditions would require copious amounts of IL if used in a continuous process making the reaction economically nonviable. The successful production of substituted ureas in a continuous process would greatly increase the space-time yield and thereby lower the production costs.

## 4.2 Results and Discussion

Mesoporous silica with a well defined pore diameter was functionalised with the imidazolium fragments seen in Figure 2 and characterised through $N_2$-physisorption, ATR-FTIR and thermo-gravimetric analysis. Silicas functionalised with [SBIM][$MeSO_4$] and [BPIM][$MeSO_4$] was applied in solketal synthesis which will not be discussed in this thesis. [BPDHIM][Br] and [BPIM][Br] functionalised silicas were used as basis for SILP catalysts applied in the continuous flow liquid phase carbonylation of aniline to be discussed later in this chapter. The motivation for applying functionalised silicas as catalyst supports was the observations, that the gas-liquid phase formation of diphenyl urea would pose a challenge for the SILP catalyst in terms of stability.

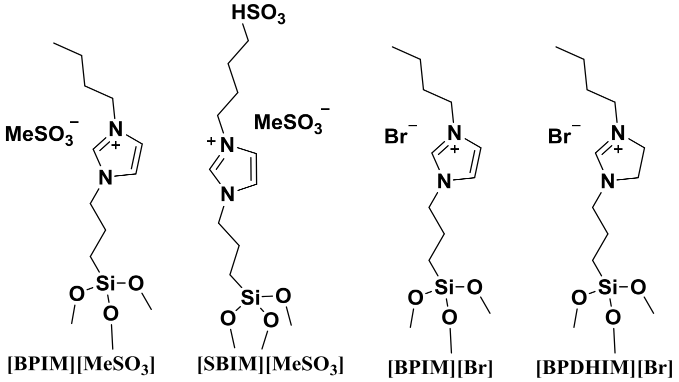


**Figure 2** Imidazolium salts anchored to silica in this chapter.

### 4.2.1 Characterization

The functionalized silicas were characterized through $N_2$-physisorption, ATR-FTIR and thermogravimetric analysis (TGA).

**Table 1.** Observed vibration bands of imidazolium salts covalently bound to silica.

| ν[$cm^{-1}$] | Vibration |
|---|---|
| 1332 | -$CH_3$ bending |
| 1418 | Asymmetric O=S=O stretch |
| 1465 | C=N stretch |
| 1565 | C=C stretch |
| 1630 | H-O-$H_{ads}$ |
| 1655 | $C_{4,5}$-H bending |
| 2877-2964 | Alkyl C-H stretch |
| 3090-3157 | $C_{4,5}$-H stretch |

The grafting of imidazolium alkoxysilanes was confirmed via ATR-FTIR. In the spectrum of the pure silica, the most pronounced vibration bands are located at 1630 cm$^{-1}$ and 2750 - 3800 cm$^{-1}$, which correspond to adsorbed water.[59–63] The material prepared by the bottom-up approach and functionalised with [SBPIM][$MeSO_3$] show only weak signal in the 1558- 1457 cm$^{-1}$ area associated with the imidazolium ring and barely visible signals in the 2750- 3800 cm$^{-1}$ associated with symmetric and asymmetric stretches of the C-H bonds in the alkyl-chains.

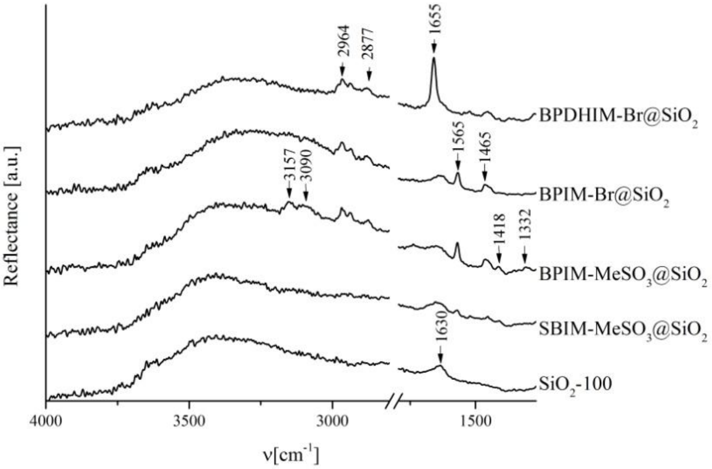


**Figure 3 ATR-FTIR** of the functionalised and non-functionalised silicas.

Using the top-down approach to functionalise the surface with [BPIM][$MeSO_3$] resulted in a material giving rise to more intense signals. The vibrations located at 3157 cm$^{-1}$ and the soft peak at 3090 cm$^{-1}$ are assigned to symmetric and asymmetric $C_{4,5}$-H stretch respectively.[35,64,65] Vibration bands at 2964 cm$^{-1}$ and 2877 cm$^{-1}$ associated with the symmetric and asymmetric C-H stretching modes of methylene and methyl groups in the alkyl-chains are clearly visible.[35,65] Bands at 1564 cm$^{-1}$ and 1455 cm$^{-1}$ correspond to C=C and C=N stretching modes associated with the imidazolium ring.[35,64] The spectrum also contain vibration bands originating from the anion in form of the asymmetric O=S=O stretch mode at 1418 cm$^{-1}$ and the very weak -$CH_3$ bending mode at 1332 cm$^{-1}$.[63,66,67] Functionalisation of the surface with [PBIM][Br] appeared to give rise to fewer signals as the $C_{4,5}$-H stretches are no longer distinguishable and it has previously been documented that these bands are subjected to red shift and change in intensity under influence of the anion.[20,65,68,69] In the spectrum of the material functionalised with [PBDHIM][Br] the vibration of C=C at 1564 cm$^{-1}$ is missing and a strong band is observed at 1653 cm$^{-1}$ arising from the non-aromatic 4,5-dihydroimidazolium. The peak at 1653 cm$^{-1}$ is assigned to the in-plane bending mode of the protons attached to $C_4$ and $C_5$.[70,71]

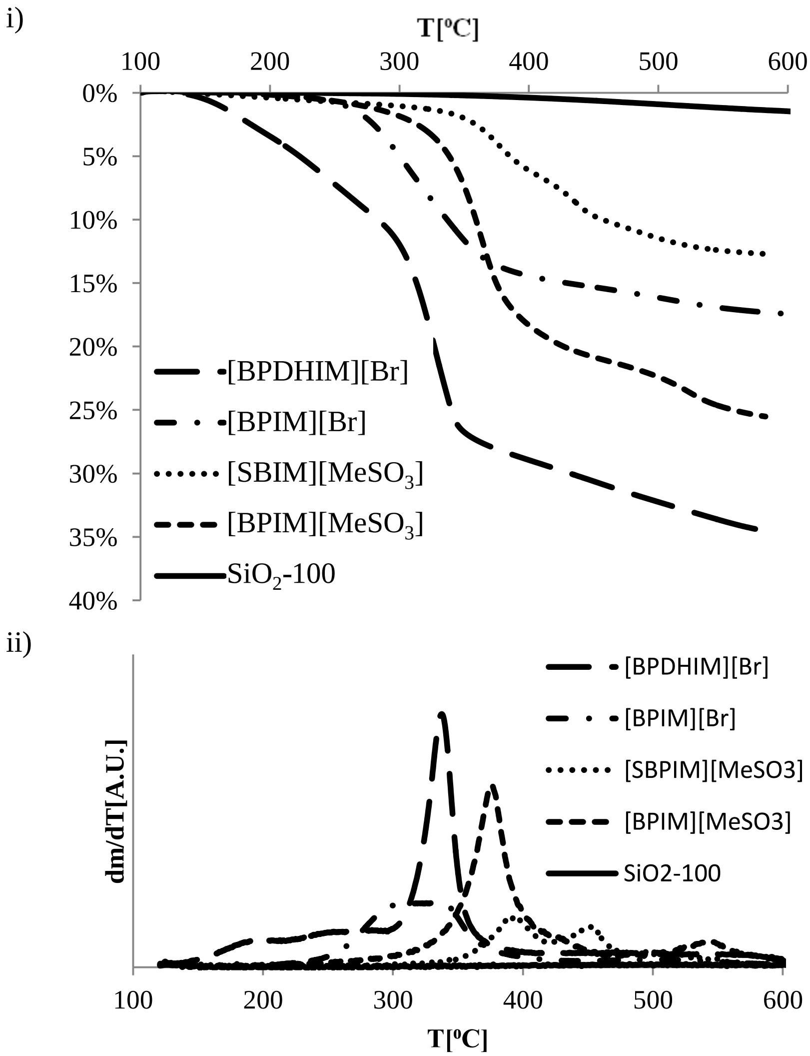


**Figure 4.** TGA analysis of the prepared supports. i) Mass loss, ii) first derivative of the mass.

The termogravimetric analysis of the functionalised materials in Table 5 shows a minimal mass loss in the case of unfunctionalised silica. The observed mass loss corresponds to gradual loss of surface hydroxyl groups. In contrast to this behaviour, the functionalised silicas undergo greater mass loss with defined decomposition temperatures. The smallest mass loss is observed for the

[SBIM][MeSO$_3$]-functionalised silica which looses 13% distributed on two decompositions at 391ºC and 451ºC corresponding to [SBIM][MeSO$_3$][40,72] and [HPIM][MeSO$_3$][23,73] respectively (Figure 4). This indicates that the N-alkylation performed with 1,4-sulfobutone was not complete prior to the protonation with methylsulfonic acid. [BPIM][MeSO$_3$]-functionalised silica synthesised by the top down method on the other hand undergo decomposition in one step at 376ºC constituting 17% of the initial mass. The peak decomposition temperature corresponds to the loss of the [BPIM][MeSO$_3$]-fragment[74,75] The slightly higher mass loss observed in the case of the [BPIM][MeSO$_3$]-functionalised material may be considered a result of the complete N-alkylation of both imidazolium-nitrogens. The mass losses observed for the [BPIM][Br]- and the [BPDHIM][Br]-functionalised silicas consists of an initial loss of water and toluene below 250ºC followed by the decomposition of the organic fragment which decrease the mass of the silica with 25% and 27%, respectively. The peak decomposition temperature of the [BPIM][Br]-functionalised material located at 335ºC is slightly higher than the 310ºC reported for [BBIM][Br].[76,77] Peak decomposition of the [BPDHIM][Br]-fragment is located slightly higher at 337ºC.

The surface area, pore volume and pore diameter of functionalized silicas is listed in Table 2. When comparing the properties of the unfunctionalised silica with the functionalized material it is seen that the grafting of different imidazolium moieties reduces the pore volume drastically from 1.00 cm$^3$/g to 0.427 m$^3$/g in the case of [BPIM][MeSO$_3$]-functionalisation, while the pore diameter are is not affected. This indicates that the [PBIM][ MeSO$_3$] anchors on the inside or at the entrance of the pores blocking part of the pores. Similar tendencies are seen for the three other functioanlisations.

**Table 2** Structural properties as effect of functionalisation.

| Silica | Functionalisation | Molar loading | $S_{BET}$[a] (m$^2$/g) | V[b] (m$^3$/g) | d[c] Å |
|---|---|---|---|---|---|
| SiO$_2$-100 | - | - | 293 | 1.00 | 105 |
| | [BPIM][MeSO$_3$] | 1.4 | 172 | 0.427 | 105 |
| | [SBIM][MeSO$_3$] | 0.6 | 219 | 0.695 | 106 |
| | [BPIM][Br] | 1.1 | 220 | 0.552 | 93.3 |
| | [BPDHIM][Br] | 1.4 | 219 | 0.619 | 88.3 |

[a]Surface area ($S_{BET}$, m$^2$/g), [b]pore volume(V, m$^3$/g), [c]BJH pore diameter (d, Å)

The functionalised silicas were used supports in the preparation of SILP catalysts for the oxidative carbonylation of aniline in continuous flow ([BPIM][Br]@SiO$_2$

and [BPDHIM][Br]@SiO$_2$) and in solketal synthesis ([SBIM][MeSO$_3$]@SiO$_2$ and [BPIM][MeSO$_3$]@SiO$_2$). The SILP catalyst was prepared by a procedure following Hermann et al.[78] and the pore-filling degree was maintained at $\alpha$=0.36 for all catalysts. In the case of a SILP supported on [BPDHIM][Br]@SiO$_2$ the deposition led to a slight decrease in surface area and pore volume, to 193 m$^2$/g and 0.553 m$^3$/g respectively, without affecting the pore diameter which was maintained at 87.3 Å. A similar patterns are observed for other SILP catalysts[79] but the reverse tendency has also been observed.[80]

**Table 3. Properties of the prepared SILP catalysts.**

| Support | IL | Pd-sourse | Pd$^a$ wt‰ | $\alpha^b$ | SILP |
|---|---|---|---|---|---|
| [BPIM][Br]@SiO$_2$ | - | [PdCl$_2$(PPh$_3$)$_2$] | 0.5 | 0.36 | SILP-1 |
| | [BPIM][Cl] | | 0.5 | | SILP-2 |
| | | | 0.05 | | SILP-3 |
| | [BPIM] [CF$_3$SO$_2$)$_2$N] | | 0.5 | | SILP-4 |
| | | | 0.05 | | SILP-5 |
| | | [PdCl$_2$(phen)] | 0.5 | | SILP-7 |
| | | [PdCl$_2$(PhNH$_2$)$_2$] | 0.5 | | SILP-11 |
| [BPDHIM][Br] @SiO$_2$ | | [PdCl$_2$(PhNH$_2$)$_2$] | 0.5 | | SILP-15 |

$^a m_{Pd}/m_{Silica+Il}$. $^b V_{IL}/V_{pore}$.

## 4.2.2 Oxidative Carbonylation of Aniline in Batch Conditions

To investigate the possibility of performing oxidative carbonylation with the modified silicas as supports for palladium catalysts the [BMIM][Br] functionalised material was impregnated with [PdCl$_2$(PPh$_3$)$_2$], and applied in batch experiments. Traditional SILPs where the IL-phase is attached through non-bonding interaction (Figure 1, (i)) have previously been observed to be leaching in liquid phase reactions[81] and covalently anchored IL's (cSILP, Figure 1 (ii)) were applied as an alternative. In a first attempt, the palladium complex was immobilized only by the anchored imidazolium-based IL which was found to give a material inactive for the reaction (non, Figure 5).

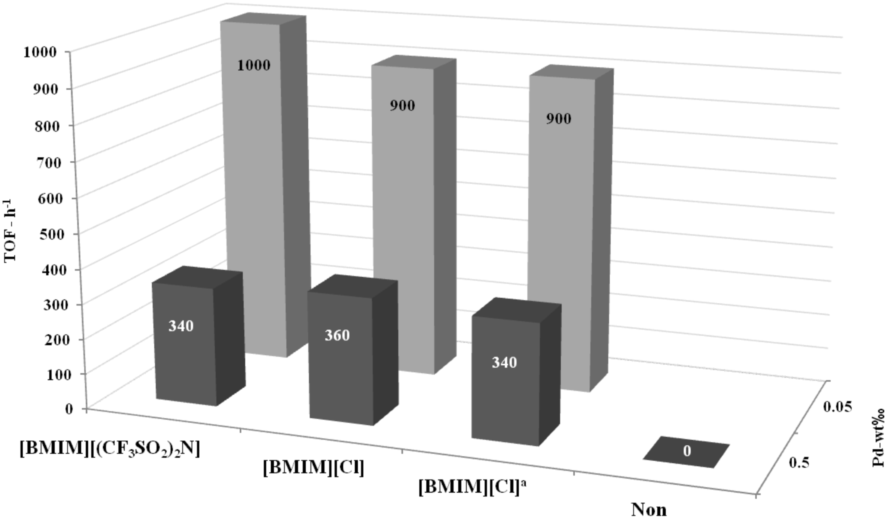
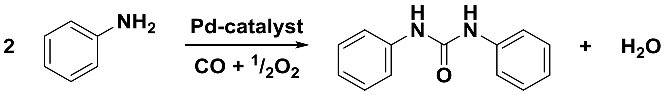
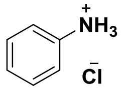
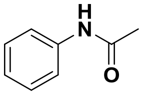


**Figure** 5 Reaction conditions: 12 mmol Aniline, 250 mg Catalyst (180-200 µm [BPIM][Br]@$SiO_2$, α=0.36, [$PdCl_2(PPh_3)_2$], 10 bar ($CO/O_2$ =9/1), 25 mL Toluene, 500 rpm, 140ºC, 1 hour. [a]Recycled catalyst.

Considering that IL/Pd(II) ratio has previously been found to be crucial for the reaction, hybrid materials with a non-bonded IL-layer on the modified silicas was prepared. The material prepared with [BMIM][Cl] and a palladium-loading of 0.5 wt‰ showed good activity and good recyclability with a TOF of 360 $h^{-1}$ in the first and 340 $h^{-1}$ in the second run ([BMIM][Cl](a), (Figure **5**). Lowering the palladium-loading to 0.05 wt‰ increased the TOF without affecting the recyclability. With the aim to utilize the spontaneous product separation observed for the biphasic experiments (see chapter 3), hybrid material was prepared with [BMIM][$CF_3SO_2)_2N$] and palladium-loadings of both 0.05 wt‰ and 0.5 wt‰. These SILP's showed TOF's of 1000 $h^{-1}$ and 340 $h^{-1}$ respectively performing similarly to the material prepared with [BMIM][Cl]. Full selectivity towards DPU was found in all experiments. During these experiments, the product was observed to crystallise on the catalyst and was extracted in refluxing toluene. In an attempt to avoid the deposition of product on the catalyst, alternative solvents were tested.

**Table 4** The influence of solvent on the selectivity.



| Entry[a] | Solvent | Conversion (%) | Selectivity (%) | By-product |
|---|---|---|---|---|
| 1 | MTBE | 44 | 78 |  |
| 2 | Toluene | 34 | >99 | - |
| 3 | EtOAc | 12 | 33 |  |

[a]Reaction conditions: 12 mmol Aniline, 300 mg SILP-2, 10 bar CO:O2 9:1, 25 mL solvent, 500 rpm, 140°C, 1 hour. [a]SILP could not be recycled.

Solvents capable of dissolving DPU, that were immiscible with the IL and with intermediate boiling points was chosen (e.g. MTBE and EtOAc) and tested in the oxidative carbonylation of aniline. Performed in MTBE (Table 4, entry 1), the reaction converted 44% of the available aniline with a selectivity of 78% towards DPU (entry 1, Table 4). In comparison, only 36% was achieved in toluene (entry 2) but with full selectivity to the desired product. When the oxidative carbonylation was performed in EtOAc, the obtained conversion was only 12%, combined with a selectivity of 33% towards DPU making N-methylbenzamide the major product. Attempts to reuse the catalyst material after reactions performed in MTBE were futile. To this end, toluene was chosen as solvent for experiments in continues flow, despite of a maximum solubility of 9 mM DPU in toluene at refluxing conditions.

### 4.2.3 Oxidative Carbonylation of Aniline in Liquid-Phase Continuous Flow Conditions

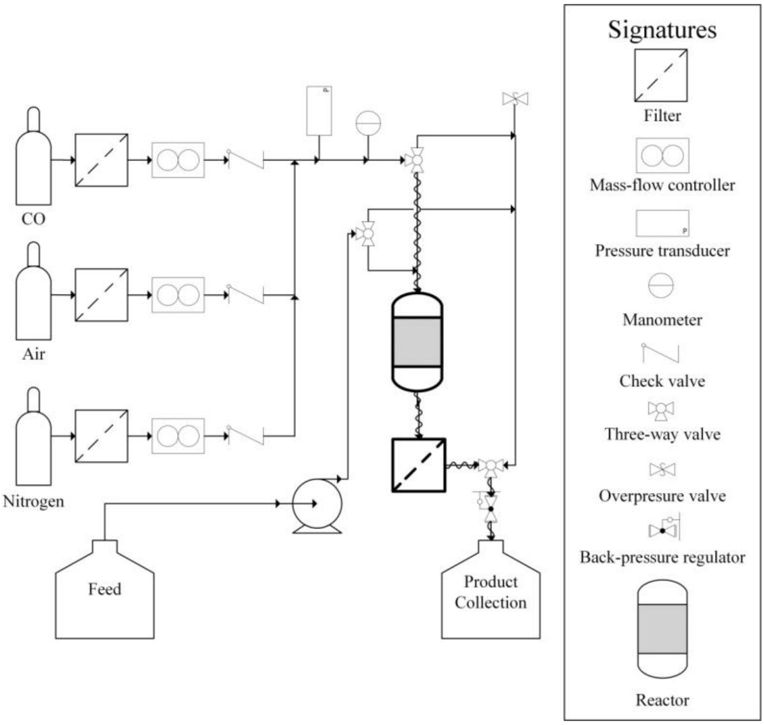


**Figure 6** Schematic overview of the flow setup used for the oxidative carbonylation of aniline.

Continuous flow oxidative carbonylation of aniline with the prepared SILP catalyst was performed 140ºC and 10 bar total pressure using fixed-bed reactor technology. The initial screening of various reaction parameters such as the catalyst loading and IL-loading quickly revealed that the primary criterion for success was catalyst stability.

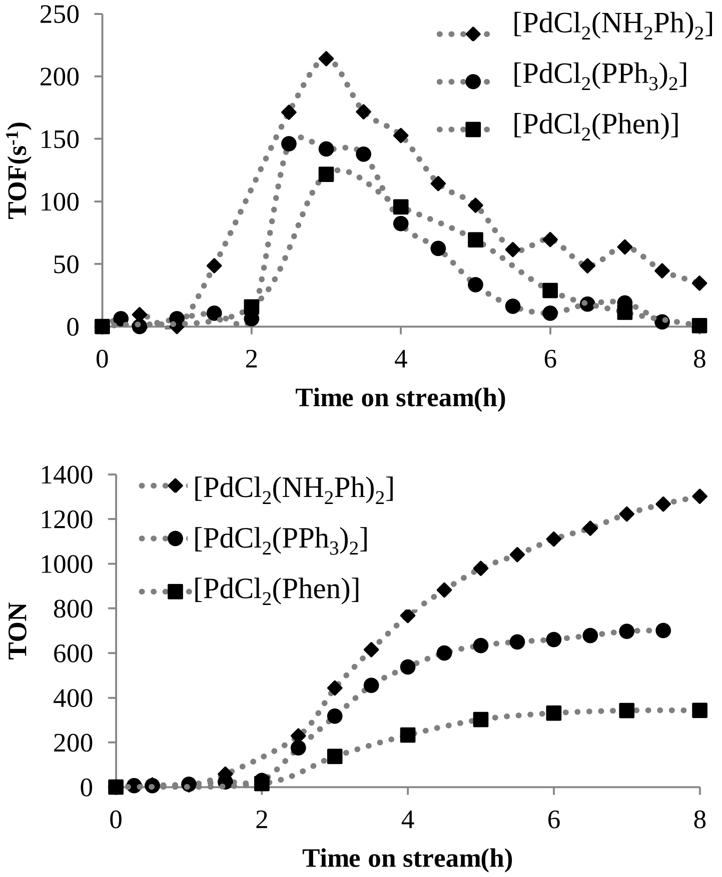


**Figure 7** The effect of the precursor on the stability of the catalyst.Reaction conditions: 250 mg catalyst(180-200 µm, α=0.36 [BMIM][$CF_3SO_2)_2N$], 0.5 wt‰ Pd(II), 1.8e-9 mol/min Aniline, 50 mL/min CO:Air =3:1, 10 bar, contact time=0.4 s, 140ºC. Top: TOF h$^{-1}$ *versus* time on stream (h), bottom: TON *versus* time on stream (h).

The performance of the prepared SILP materials with respect to activity and stability is illustrated TOF and TON. In the effort to obtain a stable catalyst the influence of the palladium precursor was investigated. In batch experiments with bulk IL only minor differences in activity was observed between [$PdCl_2(PPh_3)_2$] and [$PdCl_2(PhNH_2)_2$]. Consequently, [$PdCl_2(PhNH_2)_2$] was the first choice of precursor for the experiments in continuous flow and displayed a maximum TOF of 214 s$^{-1}$ but also a rapid deactivation despite of being substrate stabilised (Figure 7). As less strongly coordinating ligand An alternative precursor was sought in [$PdCl_2(PPh_3)_2$] which was observed to be the most active catalyst when applied in bulk IL and displayed a maximum TOF of 146 s$^{-1}$ in continuous flow. As indicated by the rapid drop in TOF values, the catalyst was not stable over time and the deactivation was ascribed to the loss of $PPh_3$ observed in the product stream. Bidentate complexes are frequently found to be more stable than their monodentate counterparts and $[PdCl_2(phen)]$ was tested in the oxidative carbonylation of aniline. With this precursor a maximum TOF of 121 $s^{-1}$ was achieved without yielding a catalyst material which was stable under the applied reaction conditions. All catalyst underwent a drastic change in colour during reaction as the previously yellow catalyst material was black after 8 hours under the applied conditions.

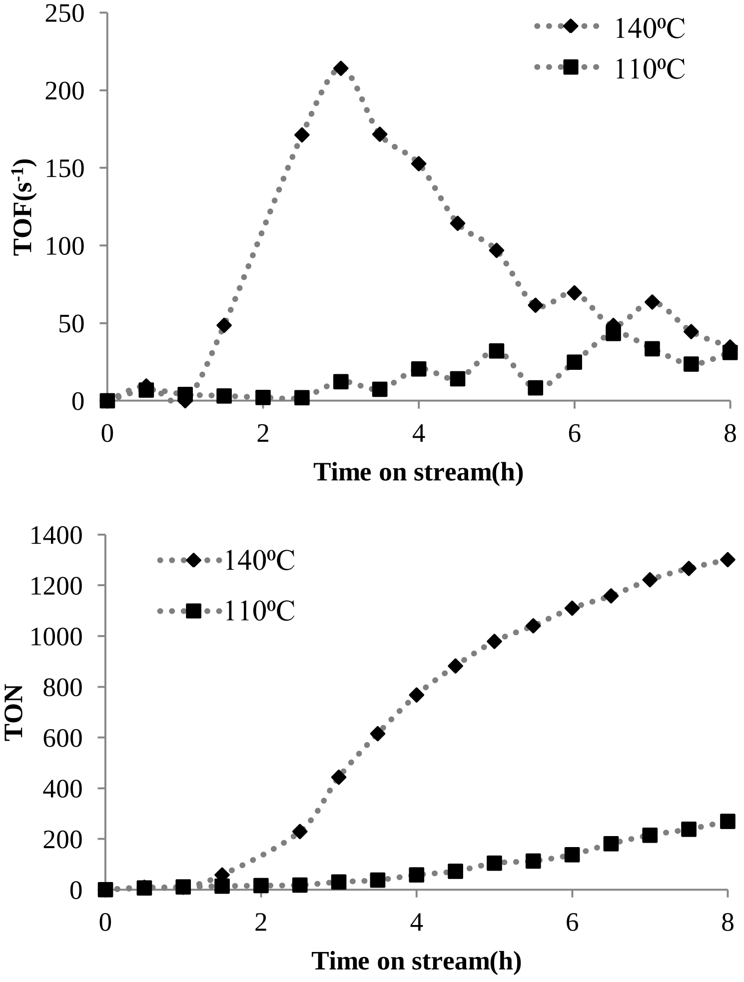


**Figure 8** The effect of temperature on the stability and performance of the catalyst. Reaction conditions: 250 mg SILP 12 (180-200 µm, α=0.36 $[BMIM][CF_3SO_2)_2N]$, 0.5 wt‰ $[PdCl_2(NH_2Ph)_2]$, [BPDHIM][BR]), 1.8e-9 mol/min Aniline, 50 mL/min CO/Air =3/1, 10 bar, contact time=0.4 s. Top: TOF $s^{-1}$ *versus* time on stream (h), bottom: Cumulative TOF *versus* time on stream (h).

In response to these observations the effect of reaction temperature was examined (Figure 8). At 140ºC, a maximum TOF of 214 $h^{-1}$ was reached followed by deactivation (Figure 8). At 110ºC a maximum TOF of 43 $s^{-1}$ was reached giving similar TOF's for the two catalysts after 8 hours on stream. The TON clearly show a flattening of the curve for the experiment performed at 140ºC whereas the TON for the experiment performed at 110ºC was still increasing after 8 hours. This shows that at 140ºC, the catalyst is losing activity while this not the case after 8 hours on stream at 110ºC. The difference in performance depending on temperature can be explained by higher stability of the catalyst at lower temperature or by slower activation and hence slower decomposition of the catalyst at lower temperature. The discoloration of the catalyst material observed after reaction at 140ºC was not observed after reaction at 110ºC.

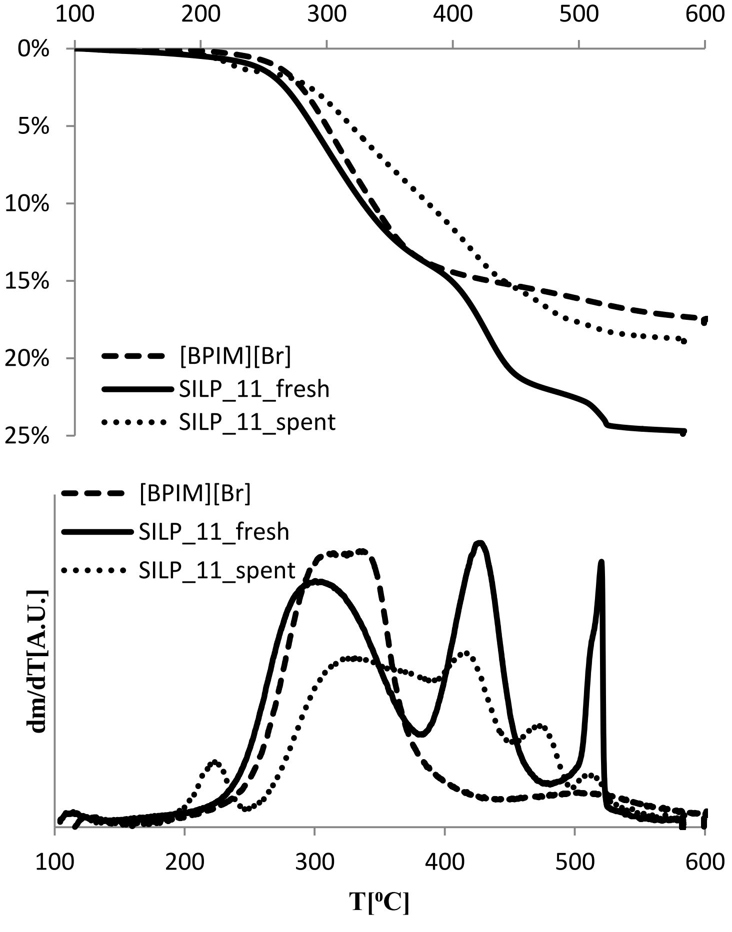


**Figure 9.** TGA analysis of the catalyst applied at 140ºC. i) Mass loss, ii) first derivative of the mass.

For the catalyst material used in the reaction at 140ºC a weight-loss of 25% during TGA analysis was observed compared to 19% for the spent catalyst indicating that a much larger part of the non-covalently anchored IL has been lost. The observed decomposition temperatures at 416ºC and 533ºC belonging to [BMIM][ $CF_3SO_2)_2N]$[82] are almost absent for the spend material while loss at temperatures associated with the decomposition of the covalently anchored IL is still observed. Mass-loss corresponding to anilinium chloride at 473ºC[83] are also observed, while the mass-loss at 218ºC is unidentified at the moment.

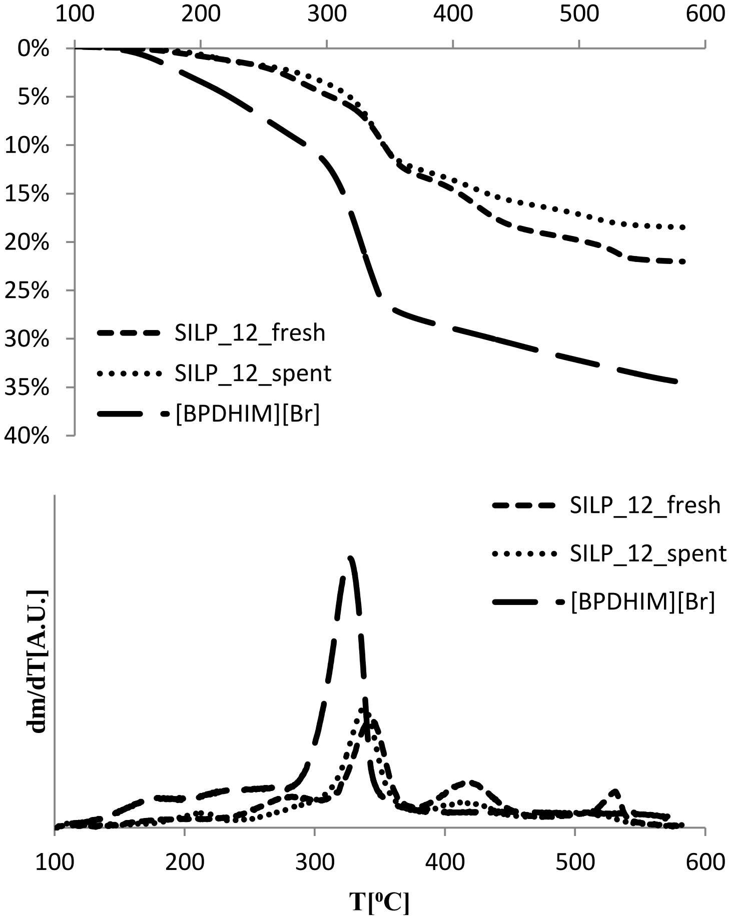


**Figure 10.** TGA analysis of the catalyst applied at 110ºC. i) Mass loss, ii) first derivative of the mass.

TGA of the spent catalyst material after reaction at 110ºC show a weight-loss of 19% compared to a weight loss of 22% for the fresh catalyst. The observed decomposition temperatures at 416ºC and 533ºC belonging to $[BMIM][CF_3SO_2)_2N]$[82] are less pronounced for the spent material in comparison to the fresh catalyst showing that the non-covalently anchored IL has been partially removed during reaction while the covalent functionalisation that decomposes at 336ºC is intact. Thus temperature has a large effect on the leaching of the IL layer on the catalyst material.

**Table 5.** Relative intensity of Pd to Si in the prepared SILP catalysts.

| | SILP-11 (cps/cps·$10^{-4}$) | SILP-12 (cps/cps·$10^{-4}$) |
|---|---|---|
| Fresh | 5.6 | 5.5 |
| Spend | 2.9 | 4.7 |

Experimental conditions: 120 mg catalyst, 180 mg $SiO_2$ 180-200 µm, 25ºC.

The fresh and spent catalysts was also analysed by X-ray flourescence spectrometry (Table 5) which indicated a satisfactory reproducibility in the catalyst preparation but the relative intensity of the Pd signal was also reduced. In the case of the catalyst applied at 140ºC 48% of the observable Pd was lost during reaction while 15% was lost during reaction at 110ºC. In combination with the catalytic results and TGA analysis this may indicate that the catalysts deactivate as a consequence of the leaching of the non-covalently bound IL leading to the loss of palladium as higher temperatures would facilitate leaching.[2]

## 4.3 Conclusion

The oxidative carbonylation of aniline was performed in under continuous flow conditions applying CO and air as the gaseous reactants and a Pd-SILP catalyst. Steady-state conditions were not obtained due to the deactivation of the catalyst. Characterization of the catalyst material after reaction indicated leaching of both palladium and non-anchored IL during the reaction to be the cause of the deactivation of the SILP catalyst. Leaching of the catalytically active components of the SILP material was most likely caused by the large amounts of solvent passed over the catalyst and the imperfect insolubility of the solvent in the catalysts. In this perspective the imidazolium functionalisation of the silica surface did not provide sufficient immobilization of the non-covalently bound IL onto the support. The applied change to the structure of the covalently anchored imidazolium was not observed to affect the leaching although a larger degree of surface funtionalisation was observed when the organic species was dihydroimidazolium. The tested Pd-complexes displayed a similar in activity as observed for experiments in bulk IL. Conclusions on their stability could not be drawn do to the leaching of the combined leaching of IL and palladium.

## 4.4 Experimental

### 4.4.1 General

Solvents were supplied by Sigma-Aldrich and dried using a Puresolv MD-7 solvent purification system prior to use when necessary. Chemicals and deuterated solvents were supplied by Sigma-Aldrich and used without any further purification. Silica supplied by Merck ( ref. no. 10184, pore 100, mesh 70-230)was fractionated to 180-200 µm particle size prior to use. NMR was performed using a Bruker 400 mHz instrument. $^1$H NMR was referenced with respect to the residual solvent signal as published by Fulmer et al.[84] DMSO; $^1$H NMR (400 mHz) δ 2.5(p, *J*=3.7, 1.8).

### 4.4.2 Characterization Techniques and Analysis

NMR analysis was performed using Varian or Oxford 400 MHz instruments. $^1$H NMR and $^{13}$C{$^1$H} NMR spectra were referenced with respect to the residual solvent peak as published by Fulmer et al.[84] $^1$H NMR (400 MHz DMSO) δ 2.5(p, *J* = 3.7, 1.8) $^{13}$C{$^1$H} NMR (100 MHz DMSO) δ 39.52.

Synthesis were monitored by GC-MS, performed using an Agilent 220-MS fitted with a HP-5, 30 m x 250 µm x 0.25 µm column.

Catalytic reactions were followed by GC-fid using an Agilent 6890N fitted with a HP-5, 30 m x 250 µm x 0.25 µm column.

ATR-FTIR was performed with a Bruker diamond-ALPHA ATR spectrometer running an exponential ATR correction. To ensure contact with the diamond pellets of the neat materials were made using a Paul Weber pellet press and 5 ton force on the material. Spectra were recorded with a resolution of 4 cm$^{-1}$.

Termogravimetric analysis (TGA) was performed on a Mettler Toledo TGA/DCS Star system. Samples were heated with a ramp of 10ºC/min. from room temperature to 100ºC and hold at 100ºC for 1 hour before heating the sample to 600ºC with a ramp of 10ºC /min. All TGA analysis were performed in dry air.

Nitrogen physisorption was performed at liquid nitrogen temperature on a Micrometrics ASAP 2020. The samples were outgassed in vacuum at 145ºC during 18 hours prior to measurement. Total apparent surface area calculated by the Brunauer-Emmet-Teller method (BET). Pore volumes were calculated based on nitrogen adsorbed at relative pressure $p/p_0$=0.95. Pore size distributions were derived using the Barret-Joyner-Halenda (BJH) method using the desorption branch.

Energy dispersive X-ray fluorescence (XRF) was performed in ten replicas on an Epsilon 3XL spectrometer using Ag, Rb and Mo filaments.

### 4.4.3 Synthesis

*1-(4-sulfobuty)l-3-(3-(silyl)propyl)-imidazolium methanesulfonate@$SiO_2$* was prepared combining the procedures published by Niknam et al.[16] and Wei et al.[40] 10 g dry silica was suspended in 20 mL toluene and refluxed with 3-(chloropropyl)triethoxysilane for 24 hours under nitrogen. The solvent was removed by filtration *via* cannula and the wet solid was washed 3 times 20 mL toluene. The wet solid was dried at 100ºC under reduced pressure. In a different flask 774 mg ( mmol) and 546 mg 50% NaH in mineral oil (mmol) was combined in 25 mL toluene and stirred 1 hour. The slurry was cannulated into 3-chloroproprylsilica and the mixture was refluxed for 24 hours. The suspension was cooled to room temperature, filtered *via* cannula and washed with 3 times 20 mL ethanol. The solid was dried overnight at 100ºC under reduced pressure. 3.4 g imidazolpropyl silica was suspended in 25 mL toluene and 144 µL (1.41 mmol) butanosultone was added *via* cannula. The mixture was stirred at 100ºC for 6 hours, cooled, filtered and washed with 3 times 10 mL toluene. The intermediate was treated with 92 µL (1.4 mmol) methylsulfonic acid in 5 mL toluene. The mixture was stirred for 24 hours and washed with 3 times 20 mL ether.

*N-(3-triethoxysilyl)propyl imidazole* was synthesised to a slightly modified procedure published by Roshan et al.[8,21] 3.4 g (50 mmol) of imidazole was suspended in 50 mL dry toluene and (3-chloropropyl)triethoxysilane 12 g (50 mmol) was added *via* canula. The mixture was refluxed overnight and the progress followed by GC-MS. The crude product was purified by column chromatography on 25 g neutral alumina (Merck 1077, Mesh 70-230) per gram crude eluding with ethyl acetate obtaining the product as a slightly viscose light yellow liquid in 30% yield.

$^1$H NMR (400 MHz, $CDCl_3$) δ 8.09 (s, 1H), 7.66 (s, 1H), 7.53 (s, 1H), 4.73 (q, *J* = 7.1 Hz, 2H), 4.59 – 4.51 (m, 2H), 4.42 (q, *J* = 7.0 Hz, 6H), 2.50 (dt, *J* = 15.3, 7.2 Hz, 2H), 1.85 (dt, *J* = 14.1, 7.1 Hz, 9H), 1.25 – 1.10 (m, 2H).

*1-butyl-3-(3-(triethoxysilyl)propyl)-imidazolium bromide* was synthesized according to a procedure published by Roshan et al.[21] N-(3-triethoxysilyl)propyl imidazole was dissolved in dry toluene (1:1 volume) and 1-bromobutane was added via canula. The mixture was refluxed overnight and solvent was removed under reduced pressure.

$^1$H NMR (400 MHz, DMSO) δ 9.33 (s, 1H), 7.82 (s, 1H), 7.42 (s, 1H), 4.38 (s, 4H), 4.24 – 3.98 (m, 9H), 3.80 – 3.57 (q, 6H), 2.01 – 1.64 (m, 4H), 1.33 – 1.18 (m, 2H), 1.13 (dd, *J* =

14.0, 6.9 Hz, 6H), 1.06 (dd, $J$ = 14.4, 7.4 Hz, 3H), 0.90 (t, $J$ = 7.4 Hz, 3H), 0.56 – 0.23 (m, 2H).

*1-butyl-3-(3-(triethoxysilyl)propyl)-4,5-dihydroxyimidazolium bromide* was synthesized as described for 1-butyl-3-(3-(triethoxysilyl)propyl)-imidazolium bromide.

*1-butyl-3-(3-(silyl)propyl)-imidazolium bromide@*$SiO_2$ was produced by grafting 1-butyl-3-(3-(triethoxysilyl)propyl)-imidazolium bromide onto silica following a procedure published by Luska et al.[35] 2.2 g silica was suspended in 12 mL toluene using standard schlenk technique and 3 mmol 1-butyl-3-(3-(triethoxysilyl)propyl)-imidazolium bromide dissolved in 10 mL dichloromethane was added via canula. Dichloromethane was removed under reduced pressure and the mixture was refluxed for 24 hours after which the solvent was filtered off and the product washed trice with dichloromethane.

*1-butyl-3-(3-(triethoxysilyl)propyl)-4,5-dihydroxyimidazolium bromide@*$SiO_2$was synthesized as described for 1-butyl-3-(3-(silyl)propyl)-imidazolium bromide@$SiO_2$.

*1-butyl-3-(3-(triethoxysilyl)propyl)-4,5-dihydroxyimidazolium methylsulfonate@*$SiO_2$ was prepared by refluxing 1-butyl-3-(3-(triethoxysilyl)propyl)-4,5-dihydroxyimidazolium bromide@$SiO_2$ with an eqimolar ammount of methyl sulfonic acid in toluene for 24 hours after which the solid was separated by filtration and washed with toluene. The absence of chloride in the prepared material was verified by XDF.

SILP catalysts were prepared by solubilising a palladium catalyst in IL. Subsequently the solution was diluted with THF and functionalised silica was suspended in the catalyst/IL solution. THF was removed at a reduced pressure of 0.4 bar and 40ºC.

### 4.4.4 Oxidative Carbonylation of Aniline in Batch Conditions

Catalytic test in batch conditions were performed in a 300 mL mechanically stirred Parr autoclave fitted with a Teflon liner. The reactor was equipped with thermocouple, manometer and heating jacket. Temperature and stirring rate were controlled from a Parr control unit. For each experimental run the reactor was loaded with catalyst, internal standard, substrate and solvent, flushed trice with CO before it was charged with 9:1 $CO/O_2$ mixture unless otherwise stated.

In a typical run the autoclave was loaded with 250 mg SILP material, 23.9 mL Toluene, 1.1 mL aniline, 168 µL mesitylene, 9 bar CO and 1 bar $O_2$ and heated to 140ºC under stirring at 500 rpm.

For all experimental runs the liquid volume of the reactor was kept at 25 mL. Temperature deviations from the set temperature were within ±3ºC. Reaction time was started when the internal temperature of the reactor reached the desired temperature. At the end of the experimental run the heating jacket was removed and the reactor was cooled to room temperature with ice. At room temperature the pressure was released and the solvent and SILP was separated by filtration. The product was extracted from the SILP material with refluxing toluene and hot filtration. The product was isolated from the toluene solution by removal of the solvent under reduced pressure. Catalytic performance was monitored by NMR and GC-MS.

### 4.4.5 Oxidative Carbonylation of Aniline in Liquid-Phase Continuous Flow Conditions

The oxidative carbonylation of aniline was conducted in a continuous-flow fixed-bed stainless steel vertical reactor (i.d.=9 mm, o.d.=1.2 mm) where the catalyst bed was held in place by a steel grid (pore diameter below 2 µm). 250 mg catalyst (180-200 µm) was loaded into the reactor and preheated to the desired temperature under flow of aniline/dodecane solution in toluene (12.5/0.25 mM, 0.15 mL/min.) and nitrogen (50 mL/min.). Once the temperature had stabilized, gas flow was switched to CO/air (4/1, volumetric ratio) with a flow rate of 50 mL/min and data collection was commenced. Toluene solution leaving the system was condensed and analyzed by GC using the internal standard method monitoring the aniline disappearance. During the entire experiment system pressure was maintained at 10 bar ±0.3 bar using a Samson 3730-2 electropneumatic valve ($K_V$=0.00063 $m^3/hr(bar)^{½}$). Catalytic performance was monitored by NMR and GC-MS.

## 4.5 References

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# Chapter 5

# General Conclusions

Pd-catalysed Carbonylations of Anilines in Ionic Liquids
Nanette Zahrtmann

In summary, two palladium catalysed reactions were studied in batch and one of the two was also studied under continuous flow conditions.

The first reaction was the preparation of benzamide from aniline. This reaction has received very little attention in literature despite the straight forward benefits offered by this reaction.

The second reaction was the oxidative carbonylation of aniline. This reaction was performed both under batch and under continuous flow conditions. Under batch conditions, the reaction was examined using homogenous palladium catalysts in bulk ionic liquid and with supported ionic liquid phase (SILP) catalysts. Both catalytic systems were highly active and supporting the homogenous catalyst onto solid support improved the recyclability of the catalyst. On the other hand, when the SILP material was applied in continuous flow, the leaching of both the ionic liquid and of palladium was observed leading to the deactivation of the system.

## 1 Preparation of Benzamide by Carbonylation of Anilines

Novel palladium-based catalytic systems for the synthesis of differently substituted N-phenylbenzamides are described. Notably, the catalytic system is additive free, robust and based on commercially available ligands. The ligands were found have a significant influence on the chemoselectivity of the reaction, most likely due to their different ability to stabilise hydride complexes. A wide range of primary anilines were efficiently converted to benzamides in high yield. The tolerance sterically hindered substrates was also examined and good obtained. Moreover a catalytic cycle accounting for the cleavage of sp2 C-N in the transformation is proposed. To the best of our knowledge this is a first example of catalytic C-N activation bond in presence of palladium without prior activation of the aniline.

## 2 Palladium Catalyzed Oxidative Carbonylation of Aniline in Ionic Liquid

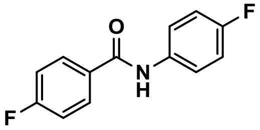
The selective oxidative carbonylation of aniline to diphenylurea was carried out in the presence of a catalytic system comprising of $[PdCl_2(PPh_3)_2]$ as catalyst and [BMIM][Cl]. TOFs up to 15600 $h^{-1}$ and 1900 $h^{-1}$ were achieved with benzoquinone and $O_2$as oxidants, respectively. The TOF achieved with benzoquinone as oxidant was, to the best of our knowledge, the highest reported to date under mild reaction conditions (140ºC and 10 bar). In order to investigate the influence of the ionic liquids, several cations and anions were applied. The best results were achieved with [BMIM][Br] while the employment of [BMIM][$(CF_3SO_2)_2N$] drove a spontaneous product separation. Unfortunately recycling experiments were not successful: The catalytic system could be reused three times but with loss of activity from the first reuse. The unexpected recycling results were attributed to the lack of stability of the palladium catalytic species during work-up of the reaction.

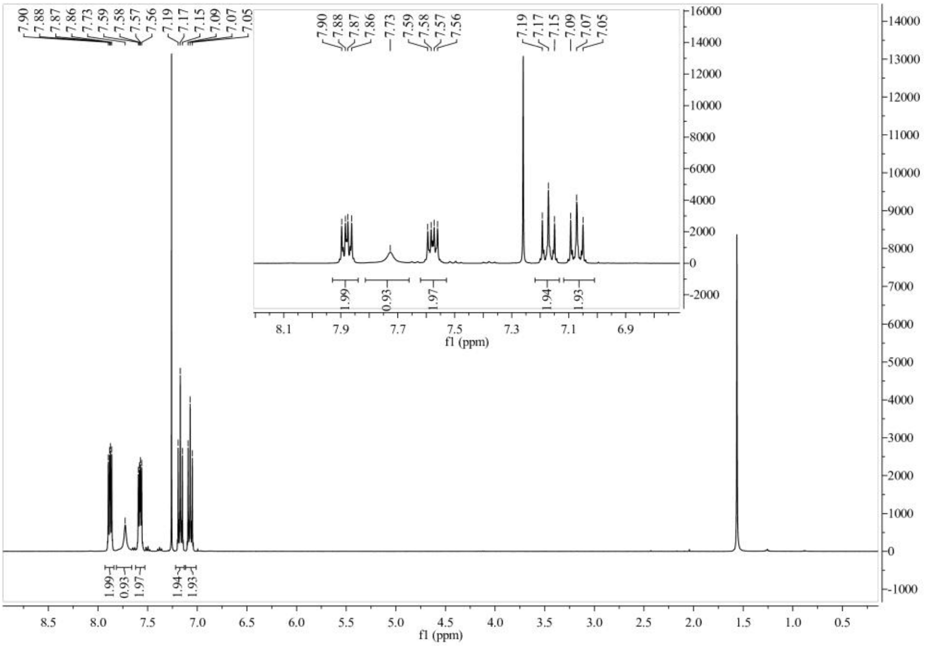
## 3 Oxidative Carbonylation of Aniline in Flow

The oxidative carbonylation of aniline was performed under continuous flow conditions applying CO and air as the gaseous reactants and a Pd-SILP catalyst. Steady-state conditions were not obtained due to the leaching of the catalyst. Characterization of the catalyst material after reaction indicated leaching of both palladium and non-anchored IL during the reaction as the cause of the deactivation of the SILP catalyst. Leaching of the catalytically active components of the SILP material was most likely caused by the large amounts of solvent passed over the catalyst and the partial miscibility of the solvent in the catalysts. In was therefore concluded that the imidazolium functionalisation of the silica surface did not provide sufficient immobilization of the non-covalently bound IL onto the support. The tested Pd-complexes displayed a similar in activity as observed for experiments in bulk IL. Conclusions on their stability could not be drawn do to the leaching of the combined leaching of IL and palladium.

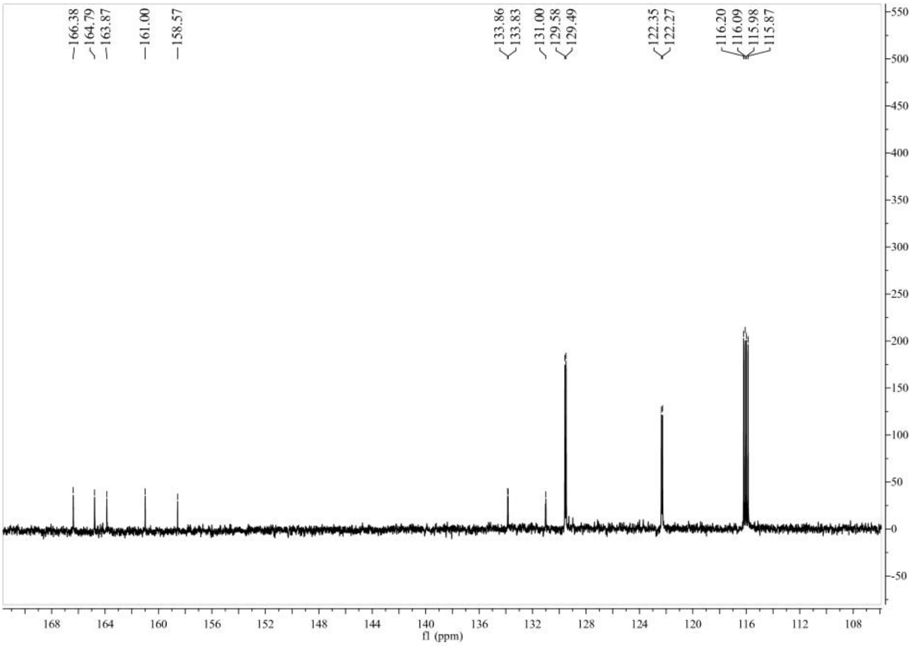
# Appendix

## A1 $^{1}$H NMR and $^{13}$C{$^{1}$H} NMR spectra of 4-Fluoro-N-(4-fluorophenyl)benzamide



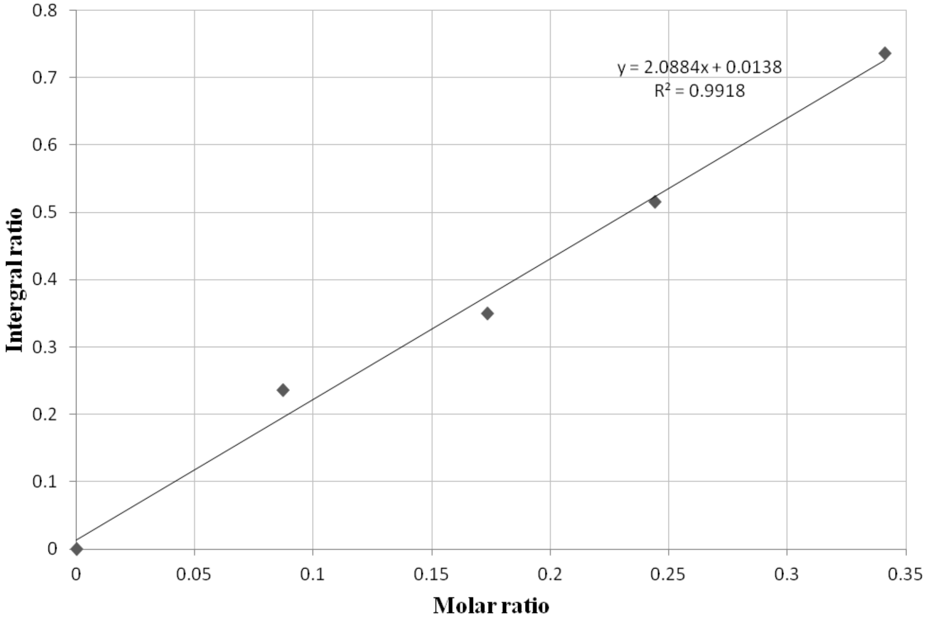


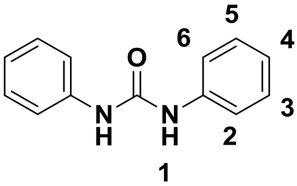
$^{1}$H NMR (CDCl$_3$, 400.13 MHz): 7.90-7.86(m, 2H), 7.73 (s, broad 1H) 7.60-7.56 (m, 2H), 7.19 (t, *J* = 8.6 Hz, 2H), 7.07 (t, *J* = 8.7 Hz, 2H).



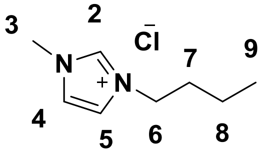
$^{13}$C NMR (CDCl$_3$, 100.61 MHz): 164.98 (d, $^{1}J_{C\text{-}F}$ = 252.9 Hz), 164,64 (s) 159.64 (d, $^{1}J_{C\text{-}F}$ = 244.2 Hz), 133.70 (d, $^{4}J_{C\text{-}F}$ = 2.9 Hz), 130.88 (d, $^{4}J_{C\text{-}F}$ = 3.1 Hz), 129.39 (d, $^{3}J_{C\text{-}F}$ = 9.0 Hz), 122.17 (d, $^{3}J_{C\text{-}F}$ =7.9 Hz), 116.00 (d, $^{2}J_{C\text{-}F}$ =11.2 Hz), 115.78 (d, $^{2}J_{C\text{-}F}$ =11.8 Hz).

## A2 Quantification by NMR





**Diphenylurea**



**[BMIM][Cl]**

$^1$H-NMR chemical shifts of the standard samples, regression coefficients of the respective protons (G) and their relaxation times (T1).

| Proton | δ[ppm] | G[s-1] | T1[s] |
|---|---|---|---|
| [BMIM][Cl] - 9 | 0.88 | 0.364549 | 2.743115 |
| [BMIM][Cl] - 8 | 1.24 | 0.47063 | 2.124811 |
| [BMIM][Cl] - 7 | 1.74 | 0.658684 | 1.518179 |
| [BMIM][Cl] - 3 | 3.38 | 0.427061 | 2.41586 |
| [BMIM][Cl] - 6 | 4.16 | 0.703238 | 1.421994 |
| DPU - 4 | 6.93 | 0.302185 | 3.309231 |
| DPU - 3,5 | 7.25 | 0.408682 | 2.44689 |
| DPU - 2,6 | 7.46 | 0.9461 | 1.056971 |
| [BMIM][Cl] - 5 | 7.72 | 0.157511 | 6.348763 |
| [BMIM][Cl] - 4 | 7.79 | 0.23184 | 4.31332 |
| [BMIM][Cl] - 2 | 9.26 | 0.258727 | 3.865078 |
| DPU - 1 | 9.67 | 1.569470 | 0.637158 |

# A3 Publications

**Brønsted Acid Ionic Liquids (BAILs) as Efficient and Recyclable Catalysts in the Conversion of Glycerol to Solketal at Room Temperature**
Gui, Zhenyou ; Zahrtmann, Nanette ; Shunmugavel, Saravanamurugan ; Reyero, Ines ; Qi, Zhiwen ; Bañares, Miguel A. ; Riisager, Anders ; Garcia Suárez, Eduardo José
in journal: ChemistrySelect (ISSN: 2365-6549) (DOI: http://dx.doi.org/10.1002/slct.201601600), vol: 1, issue: 18, pages: 5869-5873, 2016

**Palladium catalysed sp2 C-N bond activation in additive free synthesis of benzamides from primary anilines**
Lorkowski, Jan; Zahrtmann, Nanette; Garcia Suárez, Eduardo José; Godard, Cyril
in preparation

**Selective Oxidative Carbonylation of Aniline to Diphenylurea in Ionic Liquids**
Zahrtmann, Nanette; Garcia-Suárez, Eduardo José; Claver, Carmen; Godard, Cyril; Riisager, Anders
in prepartion

## A4 Conferences and Scientific Meetings

Nanette Zahrtmann, Cyril Godard, Carmen Claver, Eduardo J. Garcia-Suarez and Anders Riisager. ***Ionic Liquid Mediated Urea Synthesis.*** DTU-FAU Winter Symposium. Center for Catalysis and Sustainable Chemistry. kgs. Lyngby, January 6th 2017. Oral contribution.

Nanette Zahrtmann, Cyril Godard, Carmen Claver, Eduardo J. Garcia-Suarez and Anders Riisager. ***Pd-complex Catalysed Urea Synthesis on cSILP.*** EuChem Conference on Molten salts and Ionic Liquids. European Chemical Sciences. Vienna, July 3th – July 8th 2016. Poster and Flash oral contribution.

Nanette Zahrtmann, Cyril Godard, Carmen Claver, Eduardo J. Garcia-Suarez and Anders Riisager. **Pd-comlex Catalysed Urea Synthesis in Ionic Liquid.** 17th Nordic Symposium on Catalysis. Nordic Catalysis Society, Lund, June 14th – June 16th 2016. Oral contirbution.

Nanette Zahrtmann, Cyril Godard, Carmen Claver, Eduardo J. Garcia-Suarez and Anders Riisager. ***Ionic liquid mediated oxidative carbonylation of aniline.*** Danish Chemical Society Annual Meeting. Danish Chemical Society, Odense, June 9th 2016. Oral contribution.

Nanette Zahrtmann, Cyril Godard, Carmen Claver, Eduardo J. Garcia-Suarez and Anders Riisager. ***Pd-catalysed Urea Synthesis in Ionic Liquid.*** OMCOS18. Real Sociedad Española de Química & Institut Català d’Investigación Química, Sitges, 28. juni– 2. juli, 2015. Poster contribution.

Nanette Zahrtmann, Cyril Godard, Carmen Claver, Eduardo J. Garcia-Suarez and Anders Riisager. ***Pd-catalysed Urea Synthesis in Ionic Liquid .***GEQOXXXII. Grupo Especializado de Química Organometálica de la Real Sociedad Española de Química & Universitat Rovira i Virgili, Tarragona, 17. september – 19. september, 2014. Poster contribution.

Nanette Zahrtmann, Søren Kegnæs and Anders Riisager. ***Catalytic Reduction of Nitrate in Drinking Water.*** 247th American Chemical Society National Meeting & Exposition. American Chemical Society, Dallas TX, 16. – 20. marts 2014. Poster contribution.

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