Towards a sustainable synthesis of aromatic isocyanates : by the palladium diphosphane catalyzed reduction of nitrobenzene; a first step

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Chapter 8

Summary, conclusions, and outlook

8.1. Summary

8.1.1. General Introduction; alternative routes to TDI and MDI (Ch 1)

In Chapter 1 a summary is given of conventional and alternative strategies for the large-scale production of aromatic isocyanates such as toluene di-isocyanate (TDI) and methylene diphenylisocyanate (MDI). In the current production of TDI and MDI, phosgene is used to carbonylate an aromatic amine. Not only is phosgene extremely toxic, this process co-produces stoichiometric amounts of the corrosive hydrochloric acid; this can lead to reactor degradation and the formation of difficult to remove chlorinated side products. Despite these drawbacks, this 'phosgene route' remains the most (cost) efficient synthetic procedure and is thus still applied on the megaton scale today. Several alternative strategies for this process have been proposed over the years, and the most viable alternatives use CO as reduction and carbonylation reagent in the transition metal catalyzed reductive carbonylation of a nitro aromatic compound. In the reported studies, nitrobenzene ($PhNO_2$) is typically used as a model substrate, and the use of palladium proved to result in the most effective catalytic systems. The catalytic carbonylation of nitrobenzene is generally performed in methanol as the solvent, using homogeneous palladium complexes supported by bidentate N- or P-donor ligands. In a methanol environment, methyl phenyl carbamate (MPC) is formed (instead of phenylisocyanate) which can –in principle– be pyrolized to phenylisocyanate with the recovery of methanol.

In particular, the use of the N-donor ligand 1,10-phenanthroline (phen) with an acid co-catalyst resulted in relatively active and selective catalytic systems. As a result of these initial findings, the academic community has focussed on studying the Pd/phen/CH_3OH/H^+ –and related– catalytic systems, and catalyst turnover numbers (mol/mol) as large as ~10^5 have been reported. These studies notwithstanding, a clear and generally agreed upon mechanistic picture has yet to emerge for this reaction. Many proposals have been put forward over the years, most of which involve palladacyclic intermediates, but the apparent lack of empirical data for these proposals has hampered their firm establishment. Yet a prime paradigm in the field of homogeneous catalysis is that in order for commercially applicable catalysts to be developed, intimate knowledge of the underlying molecular mechanism of a certain reaction is essential.

A prime aim of the research described in this thesis is therefore to gain understanding into the molecular mechanism of the palladium-mediated reductive carbonylation of nitrobenzene in methanol. For these studies, diphosphane ligands were chosen as the supporting ligand for palladium; not only has the Pd/phosphane/CH_3OH system been scarcely studied, but phosphane ligands are also known to be better ligands, in particular for zero valent palladium, than N-donor ligands such as phen. In addition, their steric and electronic properties can be more easily fine-tuned than aromatic N-donor ligands. It is believed that the molecular relation between the stereo-electronic properties of the catalyst complexes and their respective catalytic performances will lead to a better mechanistic understanding necessary for the development of active and selective catalysts for a sustainable, phosgene-free, synthesis of aromatic isocyanates.

8.1.2. Catalyst precursor complex formation and structure (Ch 2)

Many of the catalytic reactions that are reported in this thesis have been carried out with catalyst precursors of the type [Pd(ligand)$(anion)_2$], wherein the supporting ligand is a bidentate diarylphosphane ligand. Such catalyst precursors are commonly synthesized *in situ,* prior to the catalytic experiment. However, for a proper interpretation of the data that arise from such catalytic experiments, it is pivotal to know whether or not the anticipated complex actually is formed. Also, intimate structural knowledge is required to link catalyst performances to their structures.

In Chapter 2 the synthetic pathways towards [Pd(ligand)$(anion)_2$] and [Pd$(ligand)_2$]$(anion)_2$ complexes is described; eighteen different ligands have been used in combination with strongly (acetate, OAc^-) or weakly (tosylate, OTs^-) coordinating anions. Of some representative complexes the solid state structure has been determined with X-ray crystallography. It is shown that the solid state structures are fully retained in solution, and that the axial positions of palladium are sterically shielded when the ligand in the complex is functionalized with oMeO substituents. The formation of [Pd(ligand)$(anion)_2$]-type complexes was studied in detail using ^{1}H- and ^{31}P-NMR spectroscopy. Depending on the ligand structure this complex is formed instantaneously, or *via* a polynuclear intermediate or it is not formed at all. It was also found that the coordinating

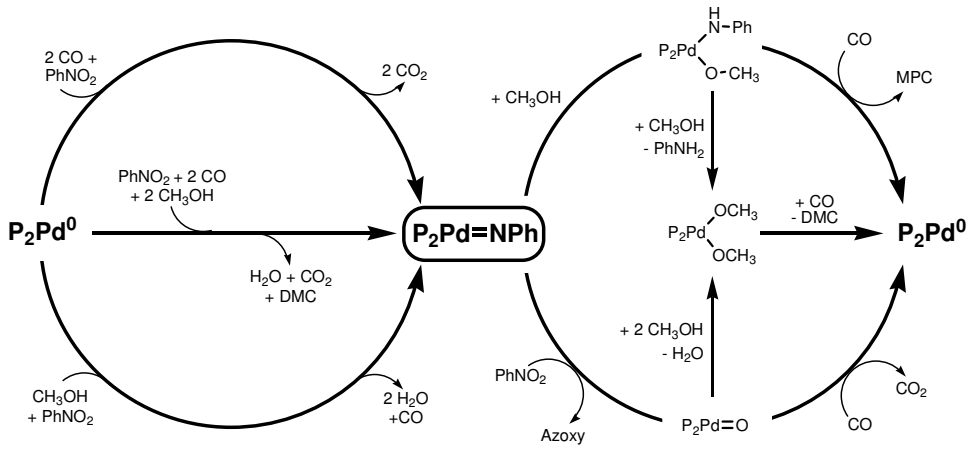
ability of the anions can alter the kinetic and/or the thermodynamic product formed.

Which complex is formed in solution is demonstrated to depend on the length and rigidity of the ligand backbone, and on the steric bulk at the ortho position of the phenyl rings on phosphorus. Notably, when the steric bulk at the ortho position of the phenyl rings on phosphorus is enlarged, complex formation is retarded and in some cases prevented altogether. This retarding effect can be overcome completely by making the backbone spacer of the ligand more rigid, which always results in instantaneous formation of the desired [Pd(ligand)(anion)$_2$] complex in methanol.

8.1.3. An unexpectedly complex network of catalytic reactions, centred around a Pd-imido intermediate (Ch 3)

In Chapter 3, the catalytic reactivity is described of palladium compounds of bidentate diarylphosphane ligands in the reaction of nitrobenzene with CO in methanol. The four ligands that were used in this study were selected partially based on the rigidity of their backbone, thus ensuring instantaneous complex formation (see Chapter 2).

Careful analysis of the reaction mixtures revealed that besides the frequently reported reduction products of nitrobenzene (MPC, *N,N'*diphenyl urea (DPU), aniline ($PhNH_2$), azobenzene (Azo) and azoxybenzene (Azoxy)), large quantities of oxidation products of methanol were co-produced as well (dimethyl carbonate (DMC), dimethyl oxalate (DMO), methyl formate (MF), H_2O, and CO). From a detailed *quantitative analysis* of the various observed reaction products, it can be concluded that several catalytic processes must operate simultaneously, coupled *via* shared catalytic intermediates. Based on simulations of observed product compositions in terms of theoretically derived stoichiometries, it was possible to determine relative weight and catalytic connectivity of the several catalytic processes occurring. It is proposed that the catalytic cycles form a complex reaction network that is centred around a palladium-imido intermediate ('P_2Pd^{II}=NPh'), as is schematically shown in Scheme 8.1.



Scheme 8.1. Overall mechanistic proposal, centered around a palladium-imido intermediate, for the catalytic coupling between nitrobenzene reduction and methanol oxidation chemistry when working with the Pd/phosphane/CH_3OH catalytic system.

Starting from an *in situ* formed P_2Pd^0 compound, oxidation to a palladium-imido compound 'P_2Pd^{II}=NPh', can be achieved by *de-oxygenation* of nitrobenzene via three different pathways (Scheme 8.1, left): with two molecules of CO (top left), with two molecules of CO and the acidic protons of two methanol molecules (centre left), or with all four hydrogen atoms of one methanol molecule (bottom left).

Formation of the imido intermediate can be followed by a protonation to form $P_2Pd^{II}(OCH_3)NHPh$ (top right) or a "disproportionation" to form Azo(xy) and 'P_2Pd=O' (bottom right). Both intermediates can be carbonylated to form respectively, MPC (top right) or CO_2 (bottom right) and re-form the initial P_2Pd^0 species to make these reactions catalytic. Alternatively, both intermediates can be protonated to form $P_2Pd^{II}(OCH_3)_2$ and aniline (top right) or water (bottom right). Carbonylation of this $P_2Pd^{II}(OCH_3)_2$ complex will produce DMC/DMO and regenerate P_2Pd^0 (centre right), allowing these reactions to proceed catalytically as well.

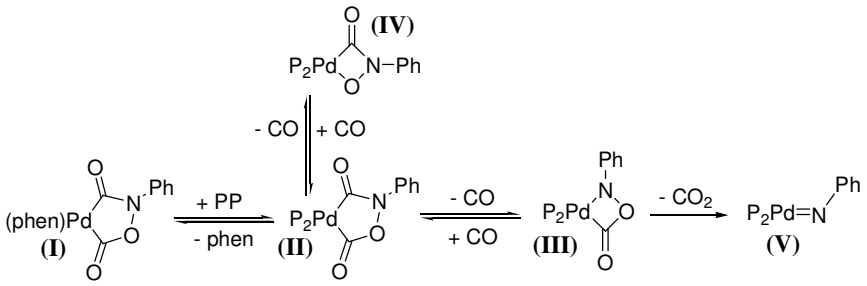
It is thus proposed that the Pd-imido species is the central key-intermediate species that links together all reduction products of nitrobenzene and all oxidation products of methanol in one unified mechanistic scheme. It has been shown that the relative occurrence of the various catalytic processes is dependent on the stereo-electronic characteristics of the catalyst, as imposed by those of the ligand.

8.1.4. A palladium-imido complex as the central product-releasing species (Ch 4)

In a mechanistic study described in Chapter 4, a variety of *in situ* formed palladium complexes of bidentate diarylphosphane ligands has been applied as catalyst precursors in the carbonylation of nitrobenzene. Variation in the length and rigidity of the backbone spacer of the chelating ligands, some carrying a methoxy-substituent on the aryl rings, was aimed to differentiate between electronic and steric effects of the catalysts' ligand on the quantitative product distribution. Additional mechanistic information has been gathered from studying the effects of reaction conditions on the product composition.

It was found that more carbonylation products (MPC and DPU) are formed relative to hydrogenation products ($PhNH_2$ and DPU) when using a ligand with smaller bite–angle (C_3–backbone) or when using a ligand with *ortho*–methoxy groups. Up to 73% of coupling products (azo(xy)benzene) was obtained when using a ligand with a larger bite–angle (C_4–backbone). Based on these observations and the dependencies of the product formation on reactant concentrations ($PhNO_2$, CO) it is proposed that, in line with the mechanistic proposal outlined in Chapter 3, formation of all aryl-containing products must compete for the same palladium–imido (P_2Pd^{II}=NPh) intermediate.

A palladacycle that is generally proposed to be the product-releasing intermediate in the Pd/phen/CH_3OH(/H^+) catalytic system (**I** in Scheme 8.2) was also considered as a possible intermediate in the Pd/phosphane/CH_3OH system (**II** in Scheme 8.2). However, as summarized in Scheme 8.2, ligand exchange reactions of the stable phen-palladacycle **I** with diphosphane ligands (studied with $^{31}P\{^1H\}$–NMR and ESI-MS) show that the formed 5–membered diphosphane-palladacycle **II** readily decomposes under mild conditions by loss of CO rather than CO_2. This eventually leads to the formation of the P_2Pd^{II}=NPh intermediate (**V**) instead of expected carbonylation products (isocyanates or MPC) after a decarboxylation of palladacycle **II**. The latter process apparently has a higher activation barrier.



Scheme 8.2. Proposed reaction sequence of the ligand exchange between palladacycle **I** and a diphosphane ligand, followed by decomposition of **II** to the imido complex **V** by initial loss of CO.

DFT calculations indicate that compound **II** indeed has a lower stability than **I**, and apparently therefore readily decomposes (by decarbonylation). The observed decrease in the rate of decomposition of the palladacycle **II** in an atmosphere of CO suggests that decarbonylation of this species proceeds by a *reversible,* low barrier carbonylation/de-carbonylation sequential process. Under certain ligand exchange conditions, additional $^{31}P\{^{1}H\}$–NMR resonances are indeed observed that can be most probably assigned to palladacycle **III**, presumably obtained via decarbonylation of palladacycle **II**. By conjecture, it is proposed that all palladacycles, **II** and **III** and **IV**, shown in Scheme 8.2 are reversibly and mutually connected by carbonylation/decarbonylation cycles. Irreversible escape from these mutually equilibrated palladacycles can only take place via decarboxylation (–CO_2) of intermediate **III** to give a palladium-imido species **V**. However, until now, the direct spectroscopic characterisation of V has remained elusive due to a rapid further decomposition under the aprotic, pressure-less conditions used in the ligand exchange model experiments, giving only a well-identified reduced Pd^{0}(diphosphane)$_2$ complex together with mainly unidentified organic products containing the 'NPh' fragment.

Proof for the possible *existence and reactivity* of a P_2Pd^{II}=NPh type species comes from a combined $^{31}P\{^{1}H\}$NMR and ESI–MS analysis of a reaction between a P_2Pd^{0} compound, containing a very bulky diphosphane ligand (1,3-bis(1,3,5,7-tetramethyl-4,6,8-trisoxa-2-phospaadamantyl)propane), and mesityl azide forming what appears to be likely a P_2Pd-imido complex (sterically) protected against rapid thermal decomposition. This complex was indeed shown to react with CO and methanol to give methyl mesityl carbamate, even under ambient mild conditions.

Under actual high CO pressure catalytic nitrobenzene carbonylation conditions in methanol as solvent, it is thought that subsequent reactions of palladium-imide **V** gives respectively, i) MPC and DPU (by methoxy- and amino-carbonylation), ii) azoxybenzene and azobenzene (by 'disproportionation' with respectively nitrobenzene and nitrosobenzene) and iii) $PhNH_2$ (by protonation by methanol) and linked formation of DMC/DMO by methanol carbonylation.

The combined catalytic and organometallic data thus all point strongly to a P_2Pd^{II}=NPh complex as *a most probable ultimately product-releasing* intermediate species under nitrobenzene carbonylation conditions.

8.1.5. Oxidative carbonylation of methanol (Ch 5)

It was disclosed in Chapter 3 that in the Pd/diphosphane/CH_3OH system, nitrobenzene reduction chemistry is catalytically coupled with methanol oxidation chemistry. The molecular aspects of these coupled reactions were studied in more detail from the perspective of nitrobenzene reduction chemistry in Chapter 4. In Chapter 5 a similar study is reported, but then from the perspective of methanol oxidation chemistry. The system is viewed from the perspective of the formation of the industrially important oxidative methanol carbonylation products DMC and DMO, for which nitrobenzene clearly functions as the terminal oxidant. It was found that the overall mechanistic insights gained by studying the reductive carbonylation of nitrobenzene (Chapters 3 and 4) apply directly to the overall mechanism for the oxidative carbonylation of methanol. In fact, the overall mechanistic scheme as shown in Scheme 8.1 reveals directly how the catalytic cycle for formation of DMC and DMO is coupled with nitrobenzene reduction chemistry. Two key intermediate stages exist in the catalytic cycle that may each evolve one equivalent of DMC/DMO relative to one $PhNO_2$ reduced.

At stage 'one', starting from P_2Pd^0, oxidative carbonylation of CH_3OH is coupled with $PhNO_2$ reduction to produce the first DMC/DMO molecule and a 'P_2Pd=NPh' species (centre left in Scheme 8.1). Formation of DMC/DMO at this stage is avoided when only CO acts as reductant (top left in Scheme 8.1), or when $PhNO_2$ reduction is coupled with CH_3OH oxidative dehydrogenation to CO (or methyl formate, bottom left in Scheme 8.1).

At stage 'two', (right in Scheme 8.1) the P_2Pd^{II}=NPh species may react in two related manners to eventually produce aniline (top right in Scheme 8.1) or Azoxy (bottom right in Scheme 8.1) respectively, and the second equivalent of DMC/DMO via a common $P_2Pd^{II}(OCH_3)_2$ complex (centre right in Scheme 8.1). The $PhNH_2$/DMC/O pathway (top right in Scheme 8.1) proceeds first *via* a $P_2Pd^{II}(OCH_3)NHPh$ complex; production of DMC/O is avoided when this complex is carbonylated to MPC. The Azoxy/H_2O/DMC/O pathway (bottom right in Scheme 8.1) proceeds first *via* a P_2Pd^{II}=O complex; the production of DMC/O is avoided when this complex is carbonylated to CO_2. All these processes are catalytic as they re-form the original P_2Pd^0 species of stage 'one'.

The selectivity for DMC relative to DMO is thought to be determined in a $[P_2PdC(O)OCH_3(R)]$–type species; the DMO/DMC ratio can be increased by increasing the CO pressure, addition of an acid, or by using a ligand with a relatively large bite-angle.

Based on the collected results, it is concluded that an ideal catalyst for oxidative carbonylation would have a relatively acidic palladium centre, be sterically undemanding in the axial positions, but sterically demanding in the equatorial positions of palladium. The palladium complex of bis(diphenylphosphanyl)-ferrocene meets these criteria and was found to use nitrobenzene as oxidant for the oxidative carbonylation of methanol most efficiently of the series studied, i.e with about 50% of the theoretical maximum efficiency with a 2:1 ratio between DMC/DMO and reduced nitrobenzene.

8.1.6. A comparative study of diphosphane and phen palladium complexes (Ch 6)

Chapter 6 reports on a comparative study of the reactivity of palladium complexes supported by phen or diphosphane ligands in the reduction of nitrobenzene, as it was found that the reactivity of palladium catalytic systems supported by phen or the bidentate diarylphospane ligand 'L4X' is remarkably similar. Both are about 70% selective for the 'PhN-containing' coupling products Azo(xy), but also produce carbonylation products (MPC and DPU) and hydrogenation products ($PhNH_2$ and DPU). In contrast, only the Pd/L4X system concurrently produces significant amounts of methanol oxidation products (DMC, DMO, MF, CO and

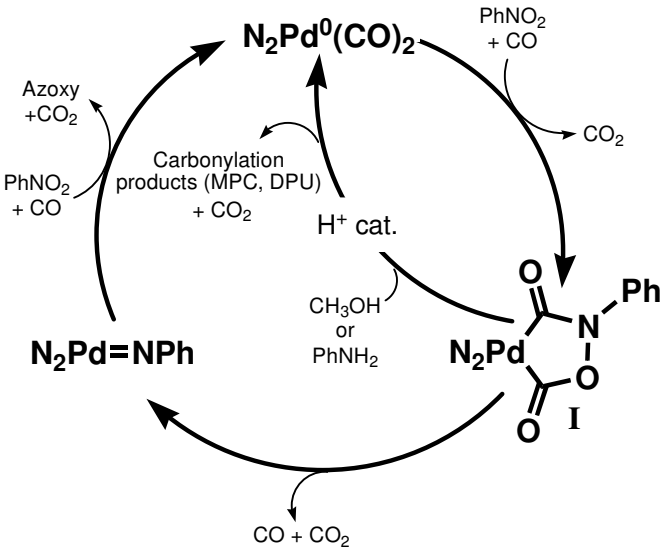
H_2O). For both the Pd/phen/CH_3OH and the Pd/L4X/CH_3OH catalyst systems, it was found that Azoxy cannot result from a condensation reaction between aniline and nitrobenzene, nor does Azoxy evolve from 'free' nitrosobenzene. Instead, it is highly plausible that Azoxy is formed by the disproportionation of nitrobenzene with a L_2Pd=NPh intermediate, as the selectivity for Azoxy depends on the nitrobenzene concentration. The possible presence of such an imido-intermediate during carbonylation experiments is corroborated by the trapping of the 'NPh' fragment in this compound by cyclohexene, resulting in the formation of the corresponding azaridine.

The palladium-imido complex L_2Pd=NPh and the 5-membered palladacycle **I/II** (see Scheme 8.2) were both considered as possible *carbonylation* product-releasing species when employing phen and L4X as the supporting ligand. However, the ESI-MS spectrum of 'phen–palladacycle', together with a ligand exchange experiment of 'phen–palladacycle' with L4X and a theoretical (DFT) study of nitrobenzene deoxygenation to L_2Pd=NPh all suggest that this 5-membered palladacycle is *not* the major carbonylation product-releasing intermediate; the barrier for decarbonylation (–CO) is lower than that of decarboxylation (–CO_2).

As a result, the palladacycle is one of several CO-equillibrated palladacycles that merely act as temporary 'PhN-reservoir', as was already disclosed for the diphosphane systems in Chapter 4. Under acidic conditions, however, the decarboxylation barrier (–CO_2) is lowered; for 'phen–palladacycle' to the point where CO_2 extrusion is favored relative to loss of CO (in line with the observations of Osborn and co-workers),[1] but for 'L4X–palladacycle' the decarbonylation (–CO) barrier is still lowest due to the destabilizing effect that this bulkier ligand apparently has on such palladacycles.

As is also illustrated in Scheme 8.3, it is concluded that i) with catalysts supported by a phen ligand de-oxygenation of nitrobenzene, in contrast with catalysts supported by the diphosphane L4X, occurs almost exclusively by CO, ii) in the absence of acid the L_2Pd=NPh complex is the dominant 'PhN' product releasing intermediate, both for diphosphane and phen based catalysts and iii) *only* under acidic conditions, 5-membered palladacycle **I** may –for the ligand phenanthroline– become the major carbonylation product-releasing intermediate.

Already substoichiometric amounts (on Pd) of acids as co-catalysts lead to a lowering of the barrier for decarboxylation, presumably initiated by protonation of the palladacycle's nitrogen atom.



Scheme 8.3. Proposed mechanism for the nitrobenzene reduction chemistry in the Pd/phen/CH_3OH(/H^+) system. N_2 = phen.

It is noteworthy that the mechanistic proposal shown in Scheme 8.3 bears strong resemblance to –but is crucially distinct from– a recent proposal by Ragaini and co-workers.[2, 3] This proposal involves first full reduction of nitrobenzene to aniline and a (phen)Pd($C(O)OCH_3$)$_2$ species (via an unknown and un-elaborated-on pathway), which is supposed to react with aniline to give MPC. The mechanistic proposal outlined in this chapter is distinctly different in that the precursors for aniline formation itself (i.e., the palladium-imido intermediate or the palladacycle **I**), are direct antecedents for MPC genesis; however, under acid-free conditions the imido-complex, generated from (**I**) via de-carbonylation and subsequent de-carboxylation, reacts predominantly with nitrobenzene to give azoxybenzene as the main product while under slightly acidic conditions palladacycle **I** decomposes by decarboxylation to form MPC in good selectivity.

The complex (phen)Pd($C(O)OCH_3$)$_2$ is then better viewed as precursor to DMC/DMO via the (aniline liberating) double protonation of the imido

intermediate. DMC and DMO were indeed found in small amounts when working under acid-free conditions, but were (in line with the data reported by Ragaini) absent when working under acidic condition; this strongly suggests that such a (phen)Pd(C(O)OCH_3)$_2$ complex is not at all formed under acidic conditions.

8.1.7. Using other nucleophiles than methanol (Ch 7)

As was outlined in Chapters 3–5, the coupling between nitrobenzene reduction chemistry and methanol oxidation chemistry in the Pd/diphosphane/CH_3OH system provided a unique and clear hint towards mechanistic details of nitrobenzene carbonylation reactions. From a more practical point of view, however, this coupling of several catalytic reactions makes the Pd/diphosphane/CH_3OH system impractically complicated when aiming only for nitrobenzene carbonylation products. For any real application in the synthesis of aromatic isocyanates to result from the research described in this thesis, it is necessary to produce carbonylation products (e.g. a carbamate or urea) more selectively.

In Chapter 7 some preliminary studies are reported that were directed at replacing methanol by respectively *p*-cresol, *i*-propanol, 2,2,2-trifluoroethanol (TFE), and aniline with the aim of preventing the oxidation reactions of the respective nucleophilic reagent. These nucleophiles were selected based on their larger size (relative to methanol) to hopefully prevent formation of the carbonate and/or oxalate; *p*-cresol and TFE were also selected for their lower nucleophilicity, in order to obtain a carbamate that is more readily pyrolized. Furthermore, the oxidative carbonylation of aniline and the reductive carbonylation of nitrobenzene are anticipated to both give the same product, namely DPU.

When employing *p*-cresol under strictly anhydrous conditions, again significant amounts of the H-containing nitrobenzene reduction products $PhNH_2$ and DPU were formed when using typical diphosphane palladium-based catalyst systems, such as either those formed from (L3)Pd$(OAc)_2$ or to a lesser extent from [Pd$(phen)_2$]$(OTs)_2$ as catalyst precursor. Qualitative analysis of obtained reaction mixtures by ^{1}H-NMR and GLC-MS, HPLC-UV/MS and of several fractions obtained after a column chromatographic separation of reaction mixtures were undertaken. From these experiments, it is concluded that *p*-cresol can, contrary to

expectations, be involved in oxidative dehydrogenation reactions to give mainly unidentified products. Mass analysis indicates formation of probably oligomeric cresylene oxides.

When using (oMeOL3X)Pd(OAc)$_2$ as catalyst precursor, and *i*-propanol was used as the nucleophilic reagent and solvent in the carbonylation of nitrobenzene, it was found that this alcohol is a most effective H-donor via oxidative dehydrogenation of *i*-propanol, thus producing mainly acetone and aniline stoichiometrically. On the other hand, while using (L3X)Pd(OAc)$_2$ as catalyst precursor oxidative carbonylation of *i*-propanol as a significant hydrogen producing process also occurs.

When using 2,2,2-trifluoroethanol (TFE) as a weakly nucleophilic reagent, an unprecedented 95% selectivity for carbamate is observed at 90% nitrobenzene conversion with (L3X)Pd(OAc)$_2$ as catalyst precursor. Moreover, the trifluoroethyl phenyl carbamate was found to readily pyrolyze to phenylisocyanate at relatively low temperatures of 200-250 °C.

Applying aniline as the nucleophilic reagent and applying a range of diphosphane ligands typically gave a full conversion of nitrobenzene with excellent selectivities for DPU. Notably, using (L3X)Pd(OAc)$_2$ as catalyst precursor, it was found that 3-methylnitrobenzene is fully converted to 3-methylaniline, with the formation of the carbonylation products DPU (90%) and DPO (10%) even when working below the transamidation temperature of 70-80 °C. From these data, together with the quantitative formation of 3-methylaniline and the absence of the unsymmetrical urea or *N,N*'-di(3-methylphenyl)urea, is was proposed that the N-aryl groups from 3-methylnitrobenzene are transferred into 3-methylaniline via an imido N-aryl ligand exchange mechanism with aniline involving the Pd-catalyst. The molecular mechanistic details of this process, the nitroarene de-oxygenation, and the formation of DPU and DPO were proposed to be very similar to those of the nitrobenzene carbonylation and methanol oxidation processes in the Pd/diphosphane/CH_3OH system (see Chapters 3 – 5).

Based on the above findings, it is concluded that *p*-cresol and *i*-propanol are inappropriate substitutes for methanol. Aniline may be a promising alternative, but the difficulties to pyrolize DPU (relative to carbamates with a good leaving

group) may render this alternative unpractical. TFE on the other hand is a promising (weakly) nucleophilic reagent to perform Pd/diphosphane catalyzed nitrobenzene carbonylation reactions, producing the corresponding carbamate in high selectivity. Facile pyrolysis of the TFE carbamate makes this an attractive platform for isocyanate synthesis, while recovering TFE.

8.2. Conclusions and outlook; one step at a time

8.2.1. General conclusions

The incentive of the work described in this thesis is the development of catalytic systems that allow phosgene to be replaced by CO in an industrial process to aromatic isocyanates such as MDI and TDI. The first step towards this goal, and the prime aim of this thesis, has been to gain intimate knowledge of the molecular mechanisms of catalytic systems in the reductive carbonylation of nitroaromatic compounds. It was expected that in the long term such molecular understanding will be an important factor for the successful development of sustainable alternative MDI or TDI synthetic pathways.

To make this first step, many different *in situ* formed diphosphane-palladium complexes of the type [Pd(ligand)(anion)$_2$] were used as catalyst precursors to study the chemistry of nitrobenzene reduction with CO in methanol. With the help of these catalytic experiments and various organometallic and DFT studies, a general mechanistic picture has emerged for this reaction in which nitrobenzene reduction chemistry is catalytically coupled with methanol oxidation chemistry by a palladium-imido intermediate. With the detailed mechanistic understanding of these processes developed in this thesis, most effects that various ligands and reaction conditions have on the course of these reactions could be rationalized.

Applying methanol as the solvent thus provided a unique opportunity to unravel a detailed molecular mechanism not only for nitrobenzene reduction chemistry, but also for methanol oxidation chemistry (Chapters 3 and 4). Moreover, the understanding of these mechanisms translates directly to closely-related catalytic systems that are hereto mainly studied in isolation of one another. Indeed, it was shown that the overall mechanistic picture can be of help to illuminate the mechanism of the oxidative carbonylation of methanol (Chapter 5), the

Pd/phen/CH_3OH(/H^+) catalyzed reductive carbonylation of nitrobenzene (Chapter 6), and the Pd-catalyzed synthesis of DPU from nitrobenzene in aniline (Chapter 7).

It is therefore concluded that the studies reported in the first chapters of this thesis unveiled a *generally applicable* mechanism for Pd-mediated nitroarene reduction chemistry, (aliphatic) alcohol oxidation chemistry, and (supposed) aniline oxidation chemistry. With this mechanistic picture, the first step has been made towards the development of optimally performing catalytic systems in alternative MDI and TDI synthetic strategies.

8.2.2. Outlook

8.2.2.1 Proposed improvements in the synthetic strategy towards TDI

In nearly all catalytic experiments described in this thesis, nitrobenzene was used as the model substrate, whereas dinitrotoluene is actually used to prepare TDI. Nevertheless, the mechanistic knowledge collected in this thesis may be used in the actual design and synthesis of more efficient catalytic systems to eventually make TDI. An obvious option is to further fine-tune the ligand in the catalyst. In this respect, bulky bidentate alkylphosphanes with a rigid backbone spacer could be studied in methanol at low temperatures (60 °C) and high CO pressure (100 bar), for several reasons: i) methanol oxidation chemistry could be blocked by applying a more basic catalyst (alkyl *vs*. aryl) and by applying a higher CO pressure; ii) the palladacycle **I** (see Scheme 8.2) is formed at merely 60 °C (in ethanol), meaning that the nitrobenzene CO-only de-oxygenation route is already operative at this temperature but is trapped in this stable palladacycle instead of decomposing to the product-releasing imido complex; iii) moreover, palladacycles such as **I** were shown to be destabilized by bulky diphosphane ligands, thus possibly allowing the application of a very mild reaction temperature, provided that the ligand is bulky enough (e.g. *t*-Bu *vs*. phenyl, >β); iv) the rigid backbone is necessary to prevent ligand dissociation, as uncoordinated alkylphosphanes will easily be oxidized by the nitroarene.

Another way towards more ideal catalytic systems is to replace the easily oxidized methanol by another nucleophilic reagent. The requirements of such a nucleophile are threefold: i) it should resist oxidation by nitrobenzene; ii) the resulting

carbamate or urea should pyrolize easily; iii) the resulting carbamate or urea should preferably crystallize from the solution to allow easy separation of the product from the homogeneous catalyst. Thus, another clear indication for further research is the systematic exploration of applying various alcohols and amines. Although *p*-cresol was discarded as a viable alternative, other phenols may be less prone to oxidation. For example pentafluorophenol cannot be oxidized to quinone-like species that are likely to be intermediately produced when using *p*-cresol as nucleophile. Also, 4-hydroxy benzoic acid may be an attractive phenol; the acidic group may act as co-catalyst, and cannot be further oxidized. As for aliphatic alcohols, only TFE seems to be a viable alterative, as other alcohols will likely also participate in oxidative carbonylation and/or dehydrogenation reactions. However, trifluoroethyl phenylcarbamate is soluble in TFE; it may thus be worthwhile to test the performance of TFE in an aprotic and relatively apolar medium such as toluene. The resulting carbamate surely is readily pyrolized and perhaps also precipitates from the apolar medium; in such a case TFE appears to be an ideal nucleophile for an alternative TDI synthesis. Using aniline as the nucleophilic reagent also gave promising results; reaching a full conversion at merely 60 °C with over 90% selectivity towards DPU, which crystallizes from aniline. However, the pyrolisis of such ureas is generally more difficult than the pyrolisis of carbamates. More importantly, it was disclosed that the N-aryl group of the nitroarene is actually converted to the amine, meaning that dinitrotoluene may well be converted to its corresponding amine with the co-production of DPU (instead of the desired di-urea). Unless this exchange of N-aryl groups can be avoided, using an aromatic amine as the nucleophile in this system is not a viable option.

8.2.2.2 Proposed improvements in the synthetic strategy towards MDI

For an alternative synthetic route towards MDI, there are two distinct strategies available, owing to the condensation reaction of two aniline molecules with formaldehyde to methylenedianiline (MDA) that is required to link two aromatic rings together. Note that nitrobenzene cannot be coupled directly to a dinitro compound due to the deactivating effect of the nitro group on the *para*-position of the aryl ring in nitrobenzene. The first strategy can be to use nitrobenzene directly as the feedstock, and carbonylate it to the corresponding carbamate or urea. The carbamate or urea may then be coupled by a condensation reaction with

formaldehyde to form the di-carbamate or di-urea; both will liberate MDI upon pyrolisis while recovering the alcohol or amine applied. In this first strategy, the proposed improvements for nitro-arene reduction chemistry made above for an alternative TDI synthesis apply directly. Additionally, instead of aniline, (tri- or penta-)fluoroaniline could be applied as nucleophile, as the resulting urea will pyrolize much easier. Questionable will be whether the nucleophilicity will remain sufficient for fluoro analogous substrates to efficiently form corresponding ureas. In addition, it is questionable whether the coupling reaction of the resulting carbamates or ureas with formaldehyde will proceed in similar yield and selectivity as the currently applied coupling of aniline to MDA. Serious obstacles that may be anticipated include the deactivation of the para-position in the carbamate or urea (relative to aniline), the possible coupling of the alcoholic group (instead of the isocyanate group), and the likely oligomerization and/or polymerization during the coupling reaction (especially when using DPU). Owing to these anticipated difficulties, it seems unlikely that nitrobenzene carbonylation is an alternative strategy in a *commercially viable* synthetic route to MDI.

Instead, the second –and probably more practical– strategy would leave the coupling reaction of aniline to MDA unperturbed and instead use MDA as its feedstock. A urea or a carbamate can then be used as an alternative to phosgene as the carbonylation reagent via transamidation reactions. In this respect, the efficient and selective catalytic synthesis of DPU (which crystallized quantitatively from aniline) may prove important. When using DPU as carbonylation reagent (synthesized via Eq. 1), MDA as feedstock (synthesized via Eq. 2), and an aromatic alcohol as the solvent (and reactant), the reaction sequence given by Equations 3 to 5 may operate, thus leading to the overall stoichiometry given by Equation 6.

$PhNO_2 + PhNH_2 + 3\ CO$	$\rightarrow DPU + 2\ CO_2$	Eq. 1
$2\ PhNH_2 + H_2C{=}O$	$\rightarrow CH_2(PhNH_2)_2 + H_2O$	Eq. 2
$CH_2(PhNH_2)_2 + 2\ DPU$	$\leftrightarrows CH_2(PhNH(CO)NHPh)_2 + 2\ PhNH_2$	Eq. 3
$CH_2(PhNH(CO)NHPh)_2 + 2\ ROH$	$\leftrightarrows CH_2(PhNH(CO)OR)_2 + 2\ PhNH_2$	Eq. 4
$CH_2(PhNH(CO)OR)_2$	$\leftrightarrows CH_2(PhNCO)_2 + 2\ ROH$	Eq. 5
		+
$2\ PhNO_2 + H_2C{=}O + 6\ CO$	$\rightarrow CH_2(PhNCO)_2 + 4\ CO_2 + H_2O$	Eq. 6

Some preliminary model studies have already been conducted to tentatively assess the viability of this proposal. As a model to the transamidation reaction described by Equation 3, DPU was reacted with 4-ethylaniline by means of a reactive distillation (in 4-ethylaniline) to remove aniline; a full conversion to the symmetrical *N,N'*-di(4-ethylphenyl)urea was observed within 45 minutes reaction time. Likewise, as a model to reaction for the transamidation reaction described by Equation 4, a reactive distillation of DPU in 3,5-dimethylphenol resulted in an 80% conversion to 3,5-dimethylphenyl phenylcarbamate within about 90 minutes. Clearly, more research is required to further test the viability of this novel alternative synthetic pathway to MDI, but the above results are hopeful.

Even though an alternative, industrially applicable process to TDI or MDI has not been developed, the research described in this thesis has made an important first step by generating knowledge that can help to develop such systems. Indeed, the mechanism of nitro arene reduction chemistry is now well-understood for [Pd(ligand)(anion)$_2$]–type catalytic systems, thus opening the way to the rational design of more active and selective catalysts for the carbonylation of nitro-aromatic compounds. Moreover, the crucial importance of the nucleophilic reagent applied also unlocks a wide range of novel ventures that can lead to alternative synthetic pathways to industrially important di-isocyanates such as TDI or MDI. The first step has thus been made, and the author eagerly anticipates the new steps that will undoubtedly follow, as it is still a realistic hope that catalytic nitro arene reductive carbonylation chemistry will one day replace the dangerous and wasteful 'phosgene-routes'.

References

[1] P. Leconte, F. Metz, A. Mortreux, J. A. Osborn, F. Paul, F. Petit, A. Pillot, *J. Chem. Soc.-Chem. Commun.* **1990**, 1616.
[2] F. Ragaini, M. Gasperini, S. Cenini, L. Arnera, A. Caselli, P. Macchi, N. Casati, *Chem. Eur. J.* **2009**, *15*, 8064.
[3] F. Ragaini, *Dalton Trans.* **2009**, 6251.