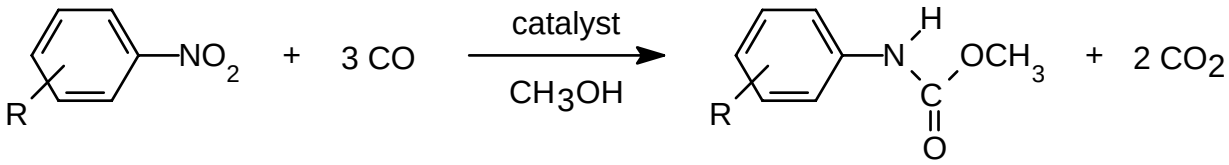
Summary

This thesis describes the palladium-catalyzed reductive carbonylation of aromatic nitro compounds; a process in which the nitro function reacts directly with CO under the influence of a palladium catalyst system. In the presence of an alcohol like methanol the corresponding carbamate is formed as main product, according to Scheme 1. Such a carbamate can be thermally cracked into the isocyanate if desired. Side products of the reaction are *N,N'*-diarylurea, an aniline derivative, an azo-, and an azoxybenzene derivative.



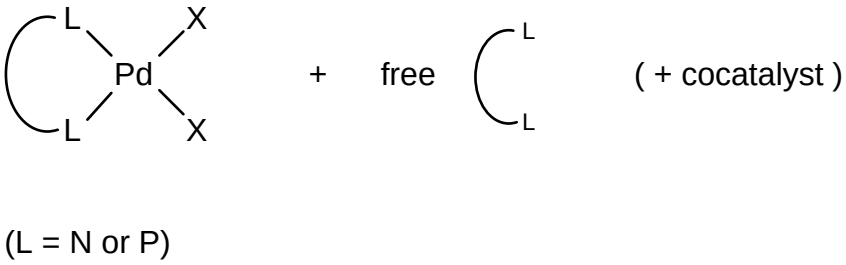
Scheme 1: Reductive carbonylation of aromatic nitro compounds.

The reductive carbonylation of the aromatic nitro compound is an alternative route to the traditional manufacturing process of aromatic isocyanates and carbamates, which uses the extremely toxic phosgene gas and produces large quantities of HCl as side product.

It was our aim to develop a stable, active, and selective homogeneous catalyst system based on palladium for the conversion of aromatic nitro compounds into their corresponding carbamates through the reaction with CO. Once an acceptable catalyst system was found for the reductive carbonylation of nitrobenzene as model substrate, this system was to be applied to a broad range of nitro substrates in order to be able to produce a series of functionalized carbamates in behalf of the fine chemical industry. The catalytic conversion of aromatic dinitro compounds could be considered as an attractive spin-off as the corresponding diisocyanates are used on large scale in the bulk chemical industry.

Chapter 1 gives an account of the importance of the aromatic isocyanates and carbamates and of the traditional and alternative production processes that have been applied so far. Furthermore, it presents a general overview of the results of the research on the palladium-catalyzed reductive carbonylation of aromatic nitro compounds between 1967 and 1992. Based on these literature reports a palladium catalyst system of the general type Pd(bidentate ligand)$(X)_2$ was chosen as subject of our study (Scheme 2).The bidentate ligand could either be a bidentate nitrogen, a bidentate phosphorus, or a mixed phosphorus-nitrogen ligand, whereas the choice of the anion X depended on the ligand that was used (e.g. acetate,

triflate). In some cases the addition of a cocatalyst like *p*-toluenesulfonic acid (*p*-tsa) was required. All types of catalyst systems are described in the Chapters 2-4.



Scheme 2: The palladium catalyst in general.

Chapter 2 deals with the influence of the donating capacity of a series of 4,4'-disubstituted-2,2'-bipyridyl ligands (R = F_3C, Cl, H, Me, MeO, and Me_2N) on the catalytic activity and selectivity of the palladium catalyst in the reductive carbonylation of nitrobenzene. Electron-withdrawing substituents on the ligand (F_3C and Cl) were found to completely deactivate the palladium catalyst, whereas bipyridyl ligands with a donating capacity higher than that of 2,2'-bipyridine (bpy) apparently do not increase the overall conversion of the substrate. Only small differences were found between the ligands with R = H, Me, MeO, and Me_2N.

If the catalyst species were generated in situ from Pd(acetate)$_2$, one of the ligands, and *p*-tsa a competition was found between Pd^{2+} and H^+ for the ligand. This competition is strongly influenced by the donating capacity of the ligand, resulting in different optimal *p*-tsa:Pd ratios for each ligand. At high *p*-tsa:Pd ratios an interesting new class of side products is formed in which additional methoxy groups are introduced at the phenyl rings of the carbamate, urea derivative, and aniline.

More active and selective catalyst systems were obtained, however, from presynthesized palladium complexes in which only noncoordinating anions were present: Pd(R_2-bpy)$_2$(OTf)$_2$. The use of Pd(R_2-bpy)Cl(OTf) complexes has clearly shown the inhibiting effect of a chloride anion.

Replacement of the bipyridyl ligands with 4,7-disubstituted-1,10-phenanthroline ligands (R = Cl, H, Me, MeO, and Me_2N) yielded more stable catalyst systems due to the better coordinating properties of the rigid phenanthroline skeleton. These systems are described in *Chapter 3*. Despite the strongly chelating skeleton still no conversion was found upon introduction of electron-withdrawing substituents (R = Cl) on the ligand. For the electron-donating substituents (R = H, Me, MeO, and Me_2N) an optimum was found at R = Me,

yielding the $Pd(Me_2\text{-phen})_2(OTf)_2$ complex as the best catalyst with a turnover frequency of 311 mol/mol/h.

Cyclic voltammetric studies on the $Pd(R_2\text{-phen})_2(Y)_2$ complexes (Y = OTf or BF_4) have established that the Pd^{II}/Pd^0 redox potential, which is thought to be very important in the catalytic cycle, is influenced by the donating capacity of the ligand, thus explaining the optimum activity at R = Me.

The donating capacity of the R_2-phen ligand also causes a subtle balance between the ligand that is applied and the particular noncoordinating anion that should be used, as the triflate anion has a slightly stronger tendency toward coordination than the perfectly symmetric tetrafluoroborate anion. The weak interaction between the palladium center and the triflate anion was also expressed by the X-ray structure of the $Pd(phen)_2(OTf)_2$ complex, as well as through various ^{1}H-NMR experiments with the different Pd/R_2-phen complexes.

In *Chapter 4* a phosphorus donor atom was introduced in the bidentate ligand in an attempt to combine the favorable influence of a phosphorus atom on the stability of the catalyst complex with the stimulating effect of the nitrogen atom on the catalytic activity. For the resulting bidentate phosphorus-nitrogen ligands it was found that the presence of weakly coordinating 2,4,6-trimethylbenzoate anions is required to obtain catalytic activity, instead of the noncoordinating anions that were preferred in the case of the bipyridyl and phenanthroline ligands. In the case of the bidentate P/N ligands containing an imine function (*N*-(2'-diphenylphosphinobenzylidene)-R-amine with R = phenyl, 4-chlorophenyl, 2,4-dimethylphenyl, 2,4-dimethoxyphenyl, and *tert*-butyl) no catalytic activity could be obtained, not even in the presence of these weakly coordinating anions. The P/N ligands in which the nitrogen atom was incorporated in a heteroaromatic ring system (2-(2'-(diphenylphosphino)-ethyl)pyridine and 8-(diphenylphosphino)quinoline), on the other hand, did yield moderately active catalyst systems. This difference is ascribed to suitable combination of σ-donating capacity and π^*-level of the latter, which strongly influences the Pd^{II}/Pd^0 redox potential as was found in the cyclic voltammetric studies in Chapter 3.

Oxidation of the phosphorus atom in the P/N ligands by the nitro substrate was found to work as a severely hampering factor for the catalytic activity, as was confirmed for a series of bidentate phosphorus ligands as well.

Within the series of bidentate phosphorus ligands (dppm, dppe, dppp, dppb, dppf, 1,2-bis(diphenylphosphino)benzene, 1,8-bis(diphenylphosphino)naphthalene, bis(2-diphenylphosphino-phenyl)ether, and 9,9-dimethyl-4,6-bis(diphenylphosphino)xanthene) the flexible systems turned out to give more efficient catalysts than their more rigid counterparts. The highest activity was obtained for dppp, because the bite angle and flexibility of this ligand allow a good stabilization of both Pd^{II} and Pd^0 intermediates.

The combined results of the catalyst tuning by the use of various ligands and anions (*Chapters 2-4*) showed that the $Pd(phen)_2(OTf)_2$/phen system is an attractive catalyst to study the scope of the reductive carbonylation of aromatic nitro compounds. *Chapter 5* presents the synthesis of a broad range of functionalized carbamates under the influence of this stable, active, selective, and readily available catalyst system.

Electron-donating substituents at the para position of nitrobenzene were found to decrease the catalytic activity as a result of the reduced oxidizing capacity of the substrate under the influence of these substituents. The selectivity toward the desired carbamate, however, increased when electron-donating substituents were used. Introduction of electron-withdrawing substituents, on the other hand, led to the production of large amounts of the azoxybenzene and azobenzene derivatives, because of the rapid formation of the nitroso intermediates from these strongly oxidizing substrates.

Steric hindrance at the ortho position of nitrobenzene caused a decrease of the catalytic activity. Yet, if the substituents were really bulky like a *tert*-butyl group reasonably fast reactions were again obtained, due to the formation of the interesting class of side products in which additional methoxy substituents are introduced on the aryl rings of the carbamates, urea derivatives, and anilines. The methoxylating side reaction was found to occur during the catalytic cycle, probably on an aniline-type of intermediate. Apparently, the reaction is enhanced by large steric hindrance on the substrate as well as by the presence of a large amount of *p*-tsa as was established in Chapter 2.

The cyano, ketone, ester, alcohol, and acid function showed to be resistant to the reaction conditions needed for the reductive carbonylation of the nitro compound, thus affording the possibility of secondary reactions after the conversion of the nitro group. Especially with 4-nitrobenzoic acid a remarkably high activity and selectivity was found (t.o.f. > 365 mol/mol/h; selectivity toward the carbamate = 94%), which gave a very convenient synthesis for *N*-protected amines containing a carboxylic acid function.

The concept of the stimulating influence of a carboxylic acid function on the catalytic behavior of the $Pd(phen)_2(OTf)_2$ catalyst complex was extended in *Chapter 6* by the use of various acids as cocatalyst for the conversion of nitrobenzene. Benzoic acids were found to greatly enhance both the catalytic activity and selectivity of the $Pd(phen)_2(OTf)_2$ catalyst. Though the effect turned out to depend on the amount of benzoic acid present in the reaction mixture, no correlation was observed with the pK_a of the acid.

Yet, the positive influence could not be equalled by other carboxylic acids or sulfonic acids. This indicates that the anions of the acidic cocatalyst play a certain role. Apparently, their coordinating abilities should be very well tuned in order to obtain the desired result. The

accelerating effect, however, is believed to be caused by the protons of the cocatalyst. Proton transfer might play a crucial role in the catalytic cycle.

The acidic cocatalyst improved the selectivity toward the desired carbamate mainly at the expense of azoxybenzene, because the accelerating effect of the protons prevents the accumulation of nitroso and nitrene intermediates that can combine to the azoxybenzene side product. The sum of urea derivative and aniline remained approximately constant under the influence of the cocatalyst, but the ratio between these two side products appeared to depend on the nature of the cocatalyst that was applied.

On the basis of the catalytic results in the presence of an acidic cocatalyst combined with the insight gained in the previous Chapters, a tentative catalytic cycle is proposed in *Chapter 6*.

Finally in *Chapter 7*, the reductive carbonylation of aromatic dinitro compounds under the influence of the $Pd(phen)_2(OTf)_2$ catalyst system was tried. These substrates are extremely important for the bulk chemical industry, but have the disadvantage that they hardly react with CO. In the absence of a cocatalyst the $Pd(phen)_2(OTf)_2$ catalyst turned out to be capable of converting the dinitro substrates into the corresponding mono-carbamate species with reasonable rates but moderate selectivities. No conversion into the desired dicarbamates could be detected. On addition of 4-chlorobenzoic acid as cocatalyst, however, both the selectivity and activity were tremendously increased. The $Pd(phen)_2(OTf)_2$/4-chlorobenzoic acid system is the first catalyst that yields acceptable rates and selectivities for the production of commercially important dicarbamates from aromatic dinitro substrates through a one-step reaction with CO.