The Pd-catalyzed semihydrogenation of alkynes to Z-alkenes: Catalyst systems and the type of active species

Drost, R.M.

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Chapter 1

General Introduction
1.1 Catalysis

Catalysis is applied to synthesis from milligram to multi-ton scale. Hence, fundamental and applied research is performed intensively to clarify catalyst mechanisms, develop new catalysts, and improve existing catalytic reactions. At the laboratory scale catalyst improvement mainly focuses on obtaining more of the desired product and benign reaction conditions. At the industrial scale catalyst improvement also means reduction of energy consumption, less waste and overall lower cost.\textsuperscript{1,2}

![Catalysts Image]

**Figure 1.** Several well-known, transition metal based catalysts.\textsuperscript{3-5}

In this thesis we focus on molecular, soluble, transition metal based catalysts. This type of catalysts possess a well-defined structure, which is built up from ligands that are coordinated to a transition metal atom (Figure 1). The coordinating ligands stabilize the metal complex. Without ligands, transition metal atoms or ions would transform to their thermodynamic most favorable state, such as bulk metal or metal oxide. Furthermore, the ligands may enhance or decrease rates of reactions by altering the steric and electronic properties of the coordination complex.\textsuperscript{2} To improve transition metal catalyzed reactions it must be understood exactly how properties of the ligand influence catalyst reactivity.

The fact that ligands can be applied to direct catalyst behavior has inspired numerous investigations of new coordinating molecules. One such a class of compounds are the N-heterocyclic carbenes. They have been combined with nearly all transition metals and the corresponding coordination compounds have been applied in a multitude of catalytic reactions.\textsuperscript{6-10} In this thesis N-heterocyclic carbenes (NHCs) are used as ligands, which are introduced in Section 1.2.

We investigate the Pd-catalyzed selective semihydrogenation of alkynes toward Z-alkenes. Z-alkenes are present in many biologically and pharmaceutically active compounds and are produced in several bulk and fine chemical processes.\textsuperscript{11-14} Therefore, the development of a convenient method for the synthesis of these compounds, especially at the laboratory scale, is intensively studied. The
semihydrogenation of alkynes is a textbook reaction. It appears to be a quite simple reaction. An alkyne is reduced to a Z-alkene and the product is obtained. However, in reality the reaction is more complicated, since many side reactions may occur. Details are discussed in Section 1.3.

Section 1.4 discusses the transfer semihydrogenation reaction. In this type of semihydrogenation of alkynes a hydrogen donor molecule is applied to circumvent the use of H₂ gas, which makes the transfer semihydrogenation reaction highly appropriate for the synthesis of the important Z-alkenes molecules at the laboratory scale.

So far we have assumed that the catalysts that were developed for the semihydrogenation reaction are molecular, well-defined species. However, it has been discovered for several reactions that nanoparticles (NPs) were formed from molecular precatalysts, and that these nanoparticles are the true catalyst (Scheme 1). Therefore, it can no longer be assumed that the type of the active catalyst is the same as that of the precatalyst. In Section 1.5 an introduction on NPs and their properties is given.

**Scheme 1.** Molecular precatalysts as a source for molecular or NP catalysts.

Determination of the type of active species is essential for the development of catalysts, as molecular and particle catalysts operate through completely different mechanisms. The determination of the type of catalyst is discussed in Section 1.6.

**1.2 N-Heterocyclic Carbene Ligands**

N-heterocyclic carbene ligands are five-membered imidazole rings that coordinate to the metal via the N-C-N carbon (Figure 2). The N-C-N motif stabilizes the imidazole-Z-ylidene species through a push-pull mechanism. The singlet carbene is stabilized through the inductive “pull” of the nitrogen atoms and additional
stabilization is obtained by donation of the lone pairs of the nitrogen atoms into the empty p-orbital of the carbene. This push-pull effect is also apparent in the resonance structures of the NHC (Figure 2). The delocalized resonance structure is the standard representation of a NHC and it is the best description of its structure. Conventional carbenes are highly reactive species. However, the stabilization effect for the imidazole-2-ylidene type carbene is so pronounced, that several NHCs can be isolated. Some of those compounds are even commercially available.

Figure 2. NHCs, their resonance structures and the stabilizing push-pull effect.

Singlet carbenes are strong sigma donors. Hence, the strong donor properties of NHC ligands were realized early on. However, over the past years it was recognized that the delocalized pi-system also contributes significantly to the binding properties of the NHC ligands. For example, the back donation from the metal into the pi*-molecular orbital can amount to up to 15% of the bonding interaction in PtII complexes.20-23 The fact that NHCs are good pi-acceptors explains why [Pd^0(NHC)] and [Ni^0(NHC)] compounds form readily.24-26 NHC ligands can thus, depending on the oxidation state of the metal, function as strongly donating and good acceptor ligands. The fact that NHCs can display such a large variation in coordination properties in organometallic complexes makes them interesting ligands for catalysts. Two famous examples where the application of NHC ligands greatly improved the catalyst properties are presented.

The first system is the Grubbs’ second generation catalyst for the alkene metathesis reaction (Scheme 2).2,27-31 The replacement of the phosphine ligands of the first generation Grubbs’ metathesis catalyst 1 for an NHC ligand led to a more active and stable second generation metathesis catalyst 2.32,33 The active catalyst is proposed to be a 14-electron species. The NHC ligand is a sterically demanding and electron donating ligand, which causes more of the complex to be in the active state. As a consequence, the Grubbs’ second generation metathesis catalyst is more active and has an expanded substrate scope compared to the first generation catalyst system. An additional advantage of the introduction of the NHC ligand is that the reactions can be performed in the presence of air and moisture.
Scheme 2. The first (1) and second (2) generation Grubbs' catalysts and three types of olefin metathesis reactions.

The second example of successful catalyst systems that apply NHCs as ligands are the pyridine-enhanced precatalyst preparation, stabilization and initiation (PEPPSI) type catalyst systems for cross-coupling reactions. Examples are the Suzuki–Miyaura, Negishi, Kumada–Tamao–Corriu and Buchwald–Hartwig–Yagupol'skii amination reactions (Scheme 3). The rate-limiting steps in standard cross-coupling reactions are oxidative addition and the reductive elimination. Application of NHC ligands can increase the reaction rates in two ways. NHCs are bulky ligands, which promote the reductive elimination step. Additionally, the strong interaction of the NHC ligand with the Pd⁰ metal center leads to an electron-rich complex that increases the rate of the oxidative addition step. The successful implementation of NHC ligands in the [Pd(SIPr)] catalyst system was supported by quantum chemical calculations system 3 (Scheme 3). The calculations showed that for the Negishi coupling the transmetallation step becomes rate-limiting, instead of the oxidative addition or the reductive elimination.
**Scheme 3.** The general mechanism for pyridine-enhanced precatalyst preparation, stabilization and initiation (PEPPSI) using a [Pd(SIPr)] precatalyst (3).

In summary, NHCs are versatile ligands. Their application in several transition metal based catalyst systems has resulted in improved applicability and reactivity. Development of catalyst systems that contain NHC ligands is actively pursued and many more successful systems are reported.\textsuperscript{7,38,39} The [Pd(\text{0}[NHC])] catalysts for the semihydrogenation reactions of alkynes to Z-alkenes are another example.\textsuperscript{40,41}

### 1.3 Selective Semihydrogenation of Alkynes to Z-alkenes

Z-alkenes are present in many biologically and pharmaceutically active compounds. The alkenes are produced both as bulk and as specialty compounds.\textsuperscript{11-14} Therefore, the development of a convenient method for the synthesis, especially at the laboratory scale, is intensely studied. Several methods have been developed, such as the Wittig,\textsuperscript{42-44} the Peterson\textsuperscript{45} and Julia\textsuperscript{46} olefination, alkene metathesis,\textsuperscript{47,48} and cross-coupling reactions.\textsuperscript{49} However, all these reactions suffer from the disadvantage that the preference for the formation of E- or Z-isomers is substrate dependent.\textsuperscript{13} The semihydrogenation reaction of alkynes is a reliable methodology to obtain pure Z-alkenes. Alkynes are highly convenient precursors for Z-alkenes, because alkynes are versatile synthetic building blocks for e.g. Sonogashira,\textsuperscript{50,51} Glaser,\textsuperscript{52,53} and Cadiot–Chodkiewicz reactions.\textsuperscript{52,54-56} Hence, alkynes can be used to form C-C bonds between
organic moieties and may subsequently be transformed into a Z-alkene (Scheme 4). This methodology is for instance applied in the synthesis of Lipoxin A.57

**Scheme 4.** Alkynes may be used as building blocks for Z-alkenes.

![Scheme 4](image)

The semihydrogenation of alkynes is discussed in every organic chemistry textbook, where it might appear to be a quite simple reaction that automatically stops after formation of the Z-alkene. However, in reality, the reaction is more complicated and many side reactions may occur (Scheme 5). For instance, the unwanted E-alkene can be formed directly from the alkyne. The alkyne can be reduced to the alkane directly, if the hydrogenation step is faster than alkene dissociation. Additionally, the product Z-alkene may re-coordinate and undergo a second reduction to the alkane. Next to over-reduction, the Z-alkene may be isomerized to the E-alkene, because for most substitutions on the alkene the E-conformation is thermodynamically favored. Finally, both the E- and Z-alkene can isomerize by shifts of the double bond in a multi-step side reaction. All these side steps make the semihydrogenation a complicated catalytic reaction. Hence, control of the chemoselectivity of the catalyst is a key issue to obtain pure Z-alkenes.

**Scheme 5.** The semihydrogenation of an alkyne to the Z-alkene and the side products.

![Scheme 5](image)

Numerous catalyst systems based on transition metals such as Rh,58 Ru,59-61 Ni,62,63 Nb,64 Cr,65 Cu66 and V67 have been investigated for the semihydrogenation reaction. The main focus for the catalytic semihydrogenation of alkynes concerns Pd as the active metal, using both molecular and particle-based catalysts.13,68-78 One of the best and most used catalyst systems for the semihydrogenation is the (improved) Lindlar's catalyst, which consists of Pd black on BaCO₃ that is treated with Pb(OAc)₂ and quinolone.13,68 However, for several types of substrates, Lindlar's catalyst displays poor activity and chemoselectivity. Especially the over-reduction of the alkene is an issue.79 Improvement of the Lindlar catalyst has proven to be difficult, and despite its drawbacks, it has been the standard hydrogenation catalyst for decades. Designing and tuning of the selectivity and reactivity of catalysts with a defined, molecular active site is generally better understood than for metal particle-based catalyst systems. Therefore, the development of molecular catalyst systems for this reaction was started by several groups.41,69,79,81
Among those systems are the $[\text{Pd}^0((\text{Ar})\text{-BIAN})(\text{L})] \ (\text{Ar-BIAN} = \text{bis(aryl)acenaphthene-quinonediiimine})$ catalysts (Figure 3). The development of these systems and the mechanistic studies of several $[\text{Pd}^0((\text{Ar})\text{-BIAN}(\text{L})]$-catalyzed reactions provide a basis for the understanding of molecular semihydrogenation catalysts.

**Figure 3.** The basic structure for the $[\text{Pd}^0((\text{Ar})\text{-BIAN})(\text{L})]$ catalysts and its proposed intermediate after heterolytic hydrogen activation.

The rigid structure and weakly donating bidentate ligand motif of the BIAN ligand combined with the low-valent metal center resulted in an extremely efficient system for the $Z$-selective conversion of alkynes to alkenes. Quantum chemical calculations showed that the BIAN ligand assists in the heterolytic splitting of molecular hydrogen over Pd-N bond, which results in a lower barrier for hydrogen activation (Figure 3, 5). This participation of the ligand may well be part of the reason for the effectiveness of this catalyst system. The catalyst performed well for aliphatic alkynes. However, conversion of alkynes with electron withdrawing substituents, such as bis-phenyl substituted alkynes, still remains a challenge.

The NHC ligands’ strong electron donating capabilities and good overlap with Pd, along with its steric bulk, are exactly the properties that should lead to successful catalysts for conversion of electron poor alkynes. Therefore, the Elsevier group developed $[\text{Pd}^0(\text{NHC})]$ catalysts for the semihydrogenation of alkynes. $[\text{Pd}^0(\text{NHC})(\text{MA})_2]$ (6), which bears two maleic anhydride (MA) ligands, was synthesized and displays good activities for challenging substrates. However, moderate $Z$-selectivities of 80% were obtained (Scheme 7).
Scheme 7. The semihydrogenation of 1-phenyl-1-propyne with 6.

A significant difference between the BIAN and NHC ligated catalysts concerns the mechanism for hydrogen activation. The BIAN ligand assists in the heterolytic splitting of hydrogen (5, Figure 3), which is not an option for the [Pd\(^{(\text{NHC})}\)] compound where the hydride has to be formed through an oxidative addition. This oxidative addition was proposed to be a difficult step in the reaction. Hence, the application of an alternative hydrogen source should improve this system. An ionic hydrogen source would transfer a hydridic type of hydrogen and a proton-like hydrogen to the catalyst and would give a catalyst mechanism that is similar to the BIAN system.

The studies on the BIAN catalyst systems have given important insights into the mechanism of the semihydrogenation reaction of alkynes. In order to improve the semihydrogenation of aryl functionalized alkenes, [Pd\(^{(\text{NHC})}\)] catalysts are proposed to be good catalysts. However, the activation of hydrogen by [Pd\(^{(\text{NHC})}\)] compounds is proposed to have a large barrier, which makes this reaction relatively slow. If this is correct, ionic hydrogen source should improve the reactivity of [Pd\(^{(\text{NHC})}\)] complexes. Therefore, the transfer semihydrogenation reaction with [Pd\(^{(\text{NHC})}\)] catalysts was developed.

1.4 Transfer Semihydrogenation Reactions

In a transfer hydrogenation reaction, the application of hydrogen is circumvented by applying a donor source that is capable of delivering hydrogen to the metal center, which transforms it to a hydride and subsequently transfers it to the substrate. In the transfer semihydrogenation reaction a 5:2 mixture of HCO\(_2\)H:NEt\(_3\) with a [Pd(DBA)]\(_3\)-CHCl\(_3\) as precursor and P(\(^t\text{Bu}\))\(_3\) as ligands were applied by Sato et al. This system performed well for aliphatic alkynes, for which the product Z-alkene was not isomerized or further reduced. However, for alkynes that are in conjugation with an aromate the reaction does not stop at the product styrenes and stilbenes, which are reduced to the alkanes after all substrate is consumed.
Our group investigated whether the *in situ* generated \([\text{Pd}^{0}(\text{IMes})(\text{MA})(\text{MeCN})]\) (7) catalyst could be applied for the transfer semihydrogenation. Catalyst 7 was successful for the transfer semihydrogenation of 1-phenyl-1-propyne using a 1:1 ratio of formic acid and triethyl amine (Scheme 8).40,41

**Scheme 8.** The Z-selective transfer semihydrogenation of 1-phenyl-1-propyne using an ionic donor pair (formic acid triethylamine).

The solvent plays an important role in obtaining high chemoselectivities. Application of MeCN, which is a stronger coordinating solvent than THF, led to excellent selectivities, also for aromatic alkynes, and no over-reduction or isomerization of Z-1-phenyl-propene was observed at full substrate conversion. Further studies towards the mechanism and substrate scope were conducted and a mechanism was proposed (Scheme 9). Starting from the *in situ* generated species 7 the coordinated solvent molecule exchanges for the alkyne. Subsequently, the formate anion coordinates by replacing MA leading to an anionic Pd⁰ complex. This species eliminates CO₂ to form the hydride species. A migratory insertion of the hydride forms the alkenyl, anionic Pd species, upon which the MA ligand recoordinates. Protonolysis with the triethyl ammonium leads to the zero-valent Z-alkene species, where a product exchange for an acetonitrile ligand regenerates the active species. The efficient exchange between the solvent and the product Z-alkene prevents the over-reduction and isomerization of the product. It is noteworthy that opposed to the semihydrogenation with molecular hydrogen this cycle does not involve a Pd¹⁺-dihydride species.

This system is highly selective, even for challenging substrates. Its most important feature is that the reaction stops when all substrate is consumed, and does not continue to give over-reduction of the product Z-alkene. This feature was previously not achieved and makes this system highly appealing for the use in laboratory organic synthesis. However, this system requires *in situ* generation of the active species under
inert conditions. This is not straightforward for non-specialized chemists, which constitutes a drawback for direct applications of this catalyst system.

**Scheme 9.** The proposed mechanism for the transfer semihydrogenation (adapted from Ref [40]).

1.5 Properties of Nanoparticles

In order to rationally design and develop catalysts, it is essential to know what the active species is. It has been discovered for several reactions\(^\text{15}\) that NPs were formed from molecular precatalysts under reaction conditions and that these NPs are the true catalysts (Scheme 1).\(^\text{16}\) The reverse, dissolution of NPs into atomic metal-, or substrate ligated active catalysts has also been reported.\(^\text{15}\) Therefore, it cannot be assumed that a molecular precatalyst gives a molecular catalyst and vice versa: the type of active species must be determined experimentally.

Transition metal based NPs range from 1-100 nm in size and are occasionally also referred to as colloids. Sometimes, NPs are confused with metal black. However, NPs may grow and aggregate to form insoluble metal black that is observed in reactions. This is not necessarily the case, several NPs were reported to be stable in solution for weeks.\(^\text{89}\) True NPs are invisible to the naked eye and may give perfectly clear solutions with colors that are not different from solutions of traditional metal complexes. The
popular belief that NPs give dark or opaque solutions is not true per se. Generally, NPs are not single compounds, but surface capped species that differ in size and shape. The chemistry of a NP occurs on the outside of the particle and its size and shape influence the reactivity of NPs. The size and shape of a NP are, in turn, determined by the interactions with (stabilizing) surface-active species. Therefore, the surface-active species are highly important for the activity and reactivity of NPs. Because most of the metal is inside the particle, relatively small amounts of surface-active species are required to stabilize NPs, and minute variations in their concentrations may have drastic effects on the catalytic activity. For this reason poor reproducibility may be an indication of active NPs. However, there are also many NP-based catalyst systems that give highly reproducible results.

1.6 Determining the Type of Active Species

Several methodologies to determine the type of active catalyst have been developed. The most influential methodology is that of Finke and co-workers. This general approach to distinguish between molecular and particle-catalysis is shown in Scheme 10 and has been successfully applied to assign the type of active catalyst of a number of systems.

Scheme 10. The Finke approach to distinguish between molecular and particle-based catalysts (adapted from Ref [94]).
The core of the approach is combining tests and techniques to obtain reliable results. The combined methods are ordered by hierarchy, where tests and techniques that yield kinetic data are the most important.

The first step consists of standard investigations such as catalyst isolation and chemical characterization. These investigations are relatively easy to perform but the interpretation is prone to errors. Transmission electron microscopy (TEM) studies for NP-detection are included in this step, and is advised to be applied early on in catalyst development studies.

The second step consists of kinetic studies such as determination of reaction rates and reaction constants. It also includes monitoring the reaction rates and selectivity of the reaction over time, and the observation and interpretation of the reactivity patterns, such as lag phases and the reproducibility of reactions. Phenomenological tests are a subclass of these reactivity studies. In these tests a quality of the catalytic reaction is monitored that is supposed to lead to different reactivities for well-defined, molecular catalysts and metal particles. The observed reactivity then indicates the type of active species.

In the third step, quantitative studies are applied, such as reaction progress kinetics and quantitative (partial) poisoning. In fourth step, additional relevant mechanistic studies are employed, such as the isolation or in situ characterization of intermediates. All data are then combined and evaluated. The true catalyst should be consistent with all data. In the case that the results of the investigations are not consistent, additional mechanistic data should be gathered that allow the assignment of the type of the active species.

Well-known studies for the determination of the active catalyst concern the Pd-catalyzed cross-coupling reactions, specifically the Heck reaction. The general mechanism is presented in Scheme 3. PdII pincer-compounds (Figure 4) were proposed to operate through a PdII-PdIV catalytic cycle. Several supported PdII SCS-pincer-compounds were developed, which were highly active at low loadings and could be recycled multiple times. Through a series of experiments it was demonstrated that the proposed PdII-PdIV cycle was incorrect. Instead a minute quantity of the molecular compound decomposed and formed NPs. Further studies even showed that these NPs are, in turn, probably only the precursors to the more active substrate ligated Pd species (Scheme 11). The work of J. G. de Vries, which is nicely summarized in his review article, provides a
mechanism for such a “Pd-cycle” in the Heck reaction. A possible mechanism for the “Pd-cycle” in the Heck reaction is shown in Scheme 11.

![Diagram of Pd precatalyst and relevant species]

**Figure 4.** The general structure of the investigated (supported) PdII SCS-pincer-precatalysts for the Heck reaction.

**Scheme 11.** A mechanism for the generation of active atomic substrate ligated Pd active species for the (ligandless) Heck reaction (adapted from Ref [98]).

The mechanism for the “Pd-cycle” in the Heck reaction shows that there are multiple species that are active and these species can transform into each other. Hence, determining the type of active catalyst may be complicated.

In summary, identification of the type of active species will not only benefit the development of well-defined, molecular catalysts, it will also lead to a better understanding of the formation of NPs. For the Heck reaction, for instance, the improved insights led to the development of catalyst systems that are highly effective at 10⁻⁶ M loadings. Therefore, the determination of the type of active catalyst is relevant for current as well as future applications in catalysis.
1.7 Scope of the Thesis

This thesis concerns studies of the Pd-catalyzed semihydrogenation of alkynes to Z-alkenes. In Chapter 2 a facile and reliable catalytic synthetic protocol for the laboratory scale synthesis of Z-alkenes is reported. The reaction produces the highly valuable Z-alkenes, which are synthetic targets for laboratory, fine and bulk scale reactions. The system developed applies a [Pd\text{II}(NHC)] precatalyst and two equivalents of PPh3. The additives increase the selectivity toward the Z-alkenes. The final system is so robust that the reaction can be performed using all solvents and reagents as received. Subsequently, in Chapter 3 the increase of the selectivity by the presence of the phosphine additive is unraveled. Based on the kinetic studies that were performed a mechanism for the “additive effect” is proposed.

The development of new NHC ligands is presented in Chapter 4. Starting from the natural amino acid histidine we report synthetic routes that provide histidine derived NHCs, histidyldienes. Several symmetrical and dissymmetrical alkyl-, benzyl-, and aryl substituted Pd\text{II} histidyldienes are synthesized. These compounds are tested as precatalysts for the transfer semihydrogenation of 1-phenyl-1-propyne.

The semihydrogenation reaction of alkynes to Z-alkenes is catalyzed by both well-defined, molecular catalysts and (nano)particles. Determining the type of active catalyst may be especially relevant for this Pd-catalyzed reaction. In Chapter 5 we set up a protocol to investigate the type of catalyst and apply it to three semihydrogenation systems: I) The Pd-catalyzed semihydrogenation of alkynes to Z-alkenes using H2 and [Pd\text{II}(NHC)] precatalysts; II) The transfer semihydrogenation of alkynes to Z-alkenes using formic acid and in situ generated [Pd\text{II}(NHC)] complexes; III) The transfer semihydrogenation of alkynes to Z-alkenes using the catalyst system that was discussed in Chapter 2. As an additional validation of the system, we also study the type of active catalyst for the co-polymerization of CO and styrene using a [Pd\text{II}(phenanthroline)] precatalyst.

1.8 References