The Pd-Catalyzed Semihydrogenation of Alkynes to Z-Alkenes: Catalyst Systems and the Type of Active Species

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Summary

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Catalysts accelerate reactions and increase their selectivity. Therefore, the development of catalysts and catalytic reactions is an important research area. A focus herein lies on transition metal based catalysts, which are often divided in homogeneous and heterogeneous catalysts. Homogeneous catalysts can be studied in much detail, which has led to in an in-depth understanding of their mechanisms.

The synthesis of *Z*-alkenes is important because these functional groups are present in many molecules. The catalytic semihydrogenation of alkynes toward *Z*-alkenes is a reaction that efficiently provides these moieties, and is relevant from bulk to laboratory scale, for instance in the synthesis of vitamin A. In this reaction many side products can be formed, therefore selectivity is a key aspect for its catalyst systems (Figure 1).

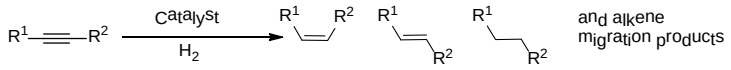

Figure 1. The semihydrogenation of alkynes to the *Z*-alkene and byproducts.

The activity and selectivity in this reaction could be improved by tuning of the molecular transition metal-based catalysts, because the mechanism of operation is often known for these catalysts. One catalyst system for the (transfer) semihydrogenation is based on a [Pd^0(NHC)]-catalyst (NHC = N-heterocyclic carbene) **1** and uses formic acid and NEt_3 as the hydrogen source (Figure 2). This system is highly selective for difficult substrates such as 1-phenyl-1-propyne.

In this thesis the semihydrogenation reaction of alkynes toward *Z*-alkenes with [PdNHC] precatalysts was studied. These studies concern the development of easy-to-use catalyst systems, the mechanism according to which they operate and the type of active species that is generated from [Pd(NHC)] complexes. **Chapter 1** provides an introduction on the topics of NHC ligands, the semihydrogenation of alkynes and methods to determine the type of catalyst.

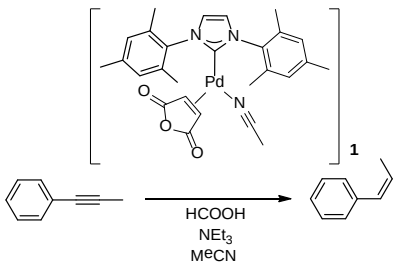

Figure 2. The transfer semihydrogenation of 1-phenyl-1-propyne to *Z*-1-phenyl-1-propene.

The transfer semihydrogenation reaction using catalyst **1** is highly suitable for laboratory scale synthesis because it does not use H_2 and it does not give over-reduction of the product *Z*-alkene after the alkyne

substrate is fully consumed. However, the catalyst has to be generated *in situ* and its preparation requires Schlenk techniques, which additional manipulations make the system less appealing to use. In **Chapter 2**, a catalyst system is developed that applies a highly stable [Pd^{II}(η^3-allyl)(IMes)] complex **2** as a precatalyst (Figure 3). The addition of PPh_3 ligands to this precatalyst results in a stable and easy-to-use system that does not involve Schlenk techniques and uses all reagents and substrates as received. This system is tolerant towards a variety of functional groups, and highly selective for a range of alkynes.

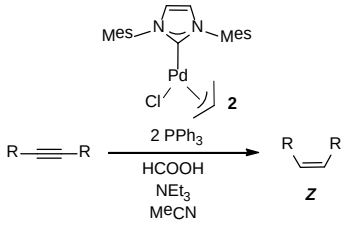

Figure 3. An easy-to-use system for the transfer semihydrogenation using a [Pd^{II}(η^3-allyl)(IMes)] (**2**) precatalyst and PPh_3 as additive ligand.

Understanding the mechanism of the additive effect of triphenylphosphine is crucial not only for the development of this specific catalyst system but for the implementation of the additive strategy in catalysis in general. In **Chapter 3** the principles that govern the additive effect are identified through a combination of mechanistic and kinetic experiments. It was found that the additive ligand increases the selectivity because it competes with binding of the Z-alkene product to a coordination site at the active Pd center, thereby preventing over-reduction.

New NHC ligands that possess more handles for functionalization allow further optimization of catalyst systems. The natural amino acid histidine is an interesting precursor for such NHCs (Figure 4).

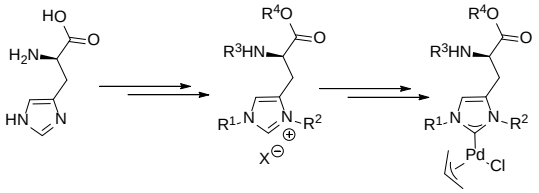

Figure 4. Histidine as a precursor for NHC (pre)catalysts for the transfer semihydrogenation.

In **Chapter 4** the development of synthetic routes for histidylidenes, NHCs derived from histidine, are described. These provide access to symmetric and dissymmetric alkyl-, benzyl- and aryl-substituted histidinium salts and both the free amine and acid can be obtained selectively. From these histidinium salts Pd^{II} histidylidene complexes were synthesized, which were tested in the transfer semihydrogenation of 1-phenyl-1-propyne. The influence of the amino acid functionality and that of the various substitution patterns on the ligand was investigated. These studies showed that a complex bearing a histidylidene ligand with hemilabile picolyl-substituents gave the best selectivity.

The semihydrogenation reaction may be catalyzed by both metal particle and molecular catalysts, which follows a different mechanism for both catalyst systems. It is important to know what type of catalyst is active, because the mechanism is used for the further development of catalyst systems. In **Chapter 5** we applied a protocol that combines quantitative partial poisoning and dynamic light scattering measurements to identify the type of the catalyst for three catalysts systems for the semihydrogenation reaction. A semihydrogenation catalyst system that applies a [Pd^0(IMes)] precatalyst (**1**) with H_2 was investigated, for which it was found that particles are the true catalysts instead of the proposed [Pd^0NHC]

complexes. Investigations of the *in situ* generated [Pd^0(NHC)] catalyst **1** with formic acid and triethyl amine (Figure 2) showed that only a small fraction of the Pd is active. Based on the results of the protocol we suggest three types of catalyst systems that could be operative. For the [Pd^{II}(NHC)] precatalyst system that was developed in **Chapters 2** and **3** (Figure 3) the protocol gave multi-interpretable results. Overall, the data from the protocol in combination with other mechanistic findings suggest that a molecular catalyst system dominates the catalytic reaction, for which part of the applied Pd is deactivated. Compared to the *in situ* generated system, the [Pd^{II}(NHC)] precatalyst with PPh_3 additives displays a significant higher percentage of active Pd. Therefore, we conclude that the PPh_3 ligands cause a stabilization of either a molecular- or nano-cluster catalyst.

For the performed (quantitative) partial poisoning studies we developed TMTU as a poisoning ligand. During these studies we demonstrated that TMTU is a superior alternative to CS_2, the standard poison, because of its beneficial properties.

The research in this thesis has demonstrated that [Pd^{II}(IMes)] precatalysts are easy-to-use selective catalyst systems when combined with additive ligands. The additive strategy can be applied to control the selectivities in this reaction. These studies also demonstrate that the type of active species in the Pd-catalyzed semihydrogenation of alkynes requires experimental determination. The protocol that was developed, is an addition to the current methods for these determinations and may also be applied to other catalyst systems.