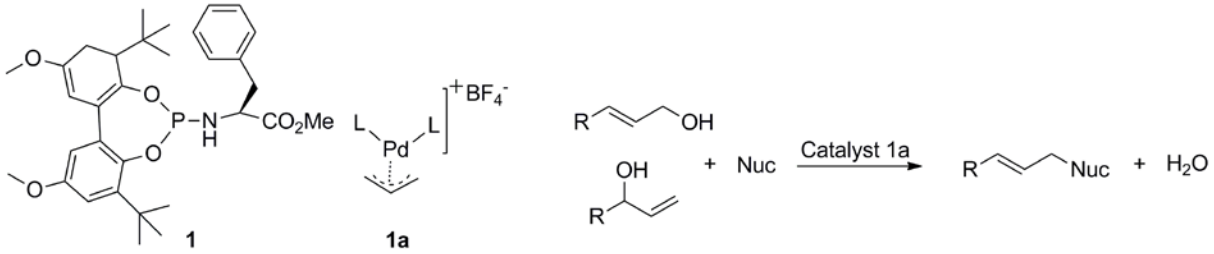
Summary

Environmental pollution is a raising problem on a global scale that will have serious consequences for the next generations, unless we act today to prevent this. Burning of fossil fuels to supply our energy demands and satisfying the material needs to sustain the growing world population are the main causes for the climate change, pollution and general depletion of natural reserves. As such, the excessive use of fossil-based carbon feedstocks should be reduced. This can be realized by large scale transformation to alternative energy sources, but also by replacing the oil-based feedstock by renewable feedstock for the preparation of chemicals and materials. Additionally, the diminishing petroleum reserves will be a major problem in the future and therefore we need to find alternatives to sustain our demand for energy, materials and economic growth. In the meantime, we should use our reserves as efficient and as carefully as possible. This implies that production processes should be waste free, if possible, and materials should be recycled as much as possible, thereby preventing further pollution. As scientists, it is our responsibility to facilitate the transition to a fully sustainable society that is in harmony with the environment. To arrive at such ideal society, scientists need to develop new catalytic tools that enable sustainable, green and clean industrial processes with a high efficiency, thus leading to less waste generation. In the perspective of developing sustainable chemical production lines, the conversion of biobased feedstocks to platform chemicals is of crucial importance and as such of growing interest. This requires the development of new (catalytic) chemical processes (e.g. dehydration, deoxygenation) to afford the desired products. The work described in this thesis has been carried out in the context of these views, as new catalytic methodology has been developed to cleanly convert allyl alcohols, a frequently encountered structural motif in biobased feedstock, and particularly in the class of terpenes.

Chapter 1 gives a general overview of the use of terpene-based feedstocks in fine chemical synthesis. Usually, these precursors need to be activated for further functionalization, a process that inherently leads to waste formation. A few reports describe strategies for the direct use of allyl-alcohols (simple derivatives of terpene-type hydrocarbons), demonstrating that these bio-based compounds in principle can be efficiently and selectively converted into a variety of valuable chemical building blocks. The content of this thesis covers the development of a novel catalytic system for the direct activation of allyl-alcohols in substitution reactions and importantly, describes a mechanistic understanding of these novel reactions.

In **Chapter 2**, we introduce a novel phosphoramidite ligand, **1**, and its Pd based catalyst, **1a**, that shows high efficiency in the direct allylic substitution reactions of allylic alcohols. The catalyst shows high selectivity for the linear isomeric products and

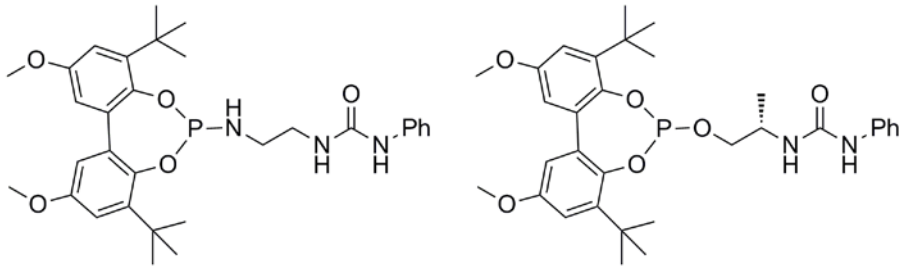
the catalyst can handle a broad substrate scope (Scheme 1). The catalyst system uses 1,3-diethylurea as a co-catalyst, which forms a bifurcated double hydrogen-bond to the palladium-bound allyl-alcohol substrate, which in turn forms a hydrogen bond to the ligands that are coordinated to Pd. This H-bond array facilitates the C-O oxidative addition process, which is the most difficult (rate-limiting) step of the catalytic cycle. We explored the scope of aromatic, aliphatic and terpene allylic alcohols in alkylation and amination reactions. Indole derivatives and various primary and secondary amines were used as the nucleophile, respectively. We have also investigated the reaction mechanism based on kinetic studies (reaction progress analysis). These studies show that the reaction is first order in the [allyl alcohol] and [1,3-diethylurea], and zero order in [nucleophile], confirming that the C-O oxidative addition step of the allyl-alcohol is the rate determining step.



Scheme 1. Schematic representation of the phosphoramidite based ligand **1** and its corresponding Pd-allyl complex, **1a**. General description of nucleophilic allylic substitution reactions of allylic alcohols.

In **Chapter 3**, we report on the study that investigated the role of urea by exploring urea-functionalized ligands in the Pd-catalyzed allylic substitution (Scheme 2). The effect of the covalently attached urea moiety of these ligands on the activation of allyl-alcohols through intramolecular H-bonding with the hydroxyl-group of the coordinated allyl-alcohol was explored. The catalysis was again performed in the presence and absence of additional 1,3-diethylurea and the results were compared with the catalytic system without a covalent bond between the ligand and a urea-moiety (**1a**+1,3-diethylurea). We expected that the covalent attachment of a urea moiety would facilitate the reaction better, for entropic reasons. However, as the general pattern, the covalent attachment of an urea-moiety did not have any beneficial effect and actually decreases the catalytic efficiency. Notably, addition of external urea still improved the catalytic activity of the urea-functionalized ligand based complexes. Catalyst **1a** (which does not contain a covalently attached urea moiety) with the aid of 1.3-diethylurea as a co-catalyst afforded the products in the highest yields in the presence of urea. Characterization of the urea-functionalized ligand complexes demonstrated the presence of a mixture of complexes in solution (some of which might be 'dormant'), which could explain the poor activity of the urea-functionalized systems. Complex **1** exists as a single species, which correlates with its higher activity.

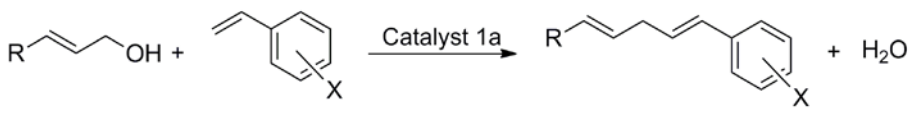
Some of the less active complexes were also shown to decompose in time, explaining the lower conversions obtained.



Scheme 2. Schematic representation of the urea-functionalized phosphoramidite and phosphite based ligands.

In **Chapter 4**, we describe our computational approach to unravel the mechanism of the allyl-alcohol based allylic amination reaction with catalyst **1a**, which operates in the presence of catalytic amount of 1,3-diethylurea as a co-catalyst. The mechanism was explored with DFT methods. In agreement with the kinetic studies reported in Chapter 2, the oxidative addition step was found to be the rate-determining step. Importantly, the role of the urea-moiety on the mechanism became clearer, as the computations showed a cooperative hydrogen bonding array between the urea moiety and the hydroxyl group of the allyl alcohol, which strengthens the hydrogen bond between the O-H moiety of the coordinated allyl-alcohol and the carbonyl-moiety of the ligand. This pattern facilitates the (rate-limiting) C-O oxidative addition step and leads to lower energy isomers throughout the catalytic cycle.

In **Chapter 5**, we report the use of catalyst **1** in direct dehydrative cross-coupling reactions with allylic alcohols and styrene derivatives (Scheme 3). The catalyst operates under additive free conditions and shows a high selectivity towards the formation of 1,4-dienes by the coupling of aromatic and aliphatic allylic alcohols with various substituted styrene derivatives. Based on kinetic studies we propose a mechanism in which the allyl-alcohol is activated by a palladium hydride, explaining why additional activators are not needed for this reaction.



Scheme 3. Direct dehydrative cross-coupling of allylic alcohols with vinyl arenes.

This thesis contributes to the development of clean chemical transformations of allyl-alcohols to a variety of valuable allyl-based compounds under additive free conditions and without stoichiometric pre-activation of the allyl-alcohol. In general, the design of novel catalysts that allow easy access to valuable (bio-based) products requires a deep understanding of the mechanism. This work also opens the door to

smart-design catalytic systems for new chemical transformations of allyl-alcohols. We anticipate that the new reactions described in this thesis, including the mechanistic knowledge will contribute to further development of these sustainable systems and design future transformation of biobased feedstocks.