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Palladium-Catalyzed Nucleophilic Substitution of Alcohols: Mechanistic Studies and Synthetic Applications

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Abstract
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This thesis deals with the palladium-catalyzed nucleophilic substitution of π-activated alcohols in which the C–O bond of a non-manipulated hydroxyl group is cleaved. The thesis is divided in two chapters describing two different catalytic systems.

Chapter 2 describes a heterogeneous palladium-catalyzed transfer hydrogenolysis of primary, secondary, and tertiary benzylic alcohols to generate the corresponding aromatic hydrocarbons using formic acid as the hydrogen donor. A detailed mechanistic investigation of this reaction has been conducted that establish the kinetic order of each reaction component and also the deuterium kinetic isotope effects. This data provide a mechanistic picture that the hydride transfer from formic acid to palladium, and not the C–O bond cleavage, is involved in the rate-determining step and that a catalytic amount of a base promotes the transfer hydrogenolysis.

Chapter 3 describes the development, mechanistic studies and synthetic scope of a homogeneous palladium-catalyzed amination of allylic alcohols. Isolation of the catalyst precursor and equilibrium studies of the palladium and π-acidic triphenylphosphite ligand show unique properties of this catalytic system. Stereochemical, kinetic, and kinetic isotope studies have been performed to provide insight into the mechanism of C–O bond cleavage of allylic alcohol and C–N bond formation catalyzed by the palladium complex. Interestingly, both O–H and C–O bond cleavages are involved in rate-determining steps.

Keywords: palladium, nucleophilic substitution, mechanism

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To my parents

List of Papers

This thesis is based on the following papers, which are referred to in the text by their Roman numerals.

I Sawadjoon, S.**;** Lundstedt, A.; Samec, J. S. M. Pd-Catalyzed Transfer Hydrogenolysis of Primary, Secondary, and Tertiary Benzylic Alcohols by Formic Acid: A Mechanistic Study. *ACS Catal.* **2013**, *3*, 635−642.

II Sawadjoon, S.; Samec, J. S. M. An atom efficient route to N-aryl and N-alkyl pyrrolines by transition metal catalysis. *Org. Biomol. Chem*. **2011**, *9*, 2548−2554.

III Sawadjoon, S.; Sjöberg P.J. R.; Orthaberc, A.; Matsson, O.; Samec, J. S. M. Mechanistic Insights into the Pd-Catalyzed Direct Amination of Allyl Alcohols: Evidence for an Outer-sphere Mechanism Involving a Palladium Hydride Intermediate. *Chem. Eur. J.* **2013** DOI: 10.1002/chem.201303431

IV Sawadjoon, S.; Orthaberc, A.; Sjöberg, P. J. R.; Eriksson, L.; Samec, J. S. M. An Initiation Study for Pd-Catalyzed Directed Allylic Aminations with Phosphite Ligands. **2013** *Submitted manuscript*

Not Included Publications

I Howard, F.; Sawadjoon, S.; Samec, J. S. M. A chemoselective route to either 4-methyl-2,4-diphenyl-2-pentene or 1,1,3-trimethyl-3-phenylindane from 2-phenylpropan-2-ol mediated by $BiBr_3$: a mechanistic study. *Tetrahedron Lett.* **2010**; *51*, 4208–4210.

II Galkin, M.; Sawadjoon, S.; Rohde, V.; Dawange, M.; Samec, J. S. M. Mild Heterogenous Palladium-Catalyzed Cleavage of β-O-4′ Ether Linkages of Lignin Model Compounds and Native Lignin in Air. *ChemCatChem*, **2013**, *in press.*

Contents

Abbreviations

Ac	Acetyl
Ar	Aryl
AIBN	Azobisisobutyronitrile
C–O bond	Carbon–oxygen single bond
Conv.	Conversion
C–N bond	Carbon–nitrogen single bond
D or d	Deuterium
Dba	Dibenzylideneacetone
Dppf	1,1′-bis(diphenylphosphino)ferrocene
Cy	Cyclohexyl
Ee	Enantiomeric excess
H	Hour(s)
ESI-MS	Electrospray ionization-mass spectrometry
HPLC	High performance liquid chromatography
KIE	Kinetic Isotope Effect
L	Ligand
M	Molar
Me	Methyl
MeCN	Acetonitrile
Mes	Mesityl
n-BuLi	*n*-Butyllithium
Net_3	Triethylamine
NMR	Nuclear magnetic resonance
Pd/C	Palladium on carbon
Ph	Phenyl
S	Second
Sec	Second
THF	Tetrahydrofuran
Ts	*p*-Toluenesulfonyl
VT	Variable temperature

Preface

The majority of this thesis was either (i) written for intent to publish or (ii) written and accepted for publication in scientific journals. Modifications to sections previously accepted for publication were made, where necessary, to format the material in a consistent manner throughout this thesis. This thesis describes the work reported in publications I-IV listed on the preceding page.

1. Introduction

1.1 Alcohols

Alcohols are organic compounds that have a carbon bound to a hydroxyl group. The word alcohol is derived from the early Arabic *al-kuhl*, meaning "the powder" and was used as eyeliner. Alcohols are abundant organic compounds that originate from biomass such as starch, lignocelluloses (cellulose, hemicellulose, and lignin),[1] and triglycerides[2] as shown in Figure 1. The conversion of biomass into fuels and value-added chemicals is currently of great interest due to the decreasing fossil fuel reserves and emerging global warming.[3] Glycerol is obtained as the main by-product in biodiesel production which is generated by a transesterification reaction of triglycerides and methanol.[4] Other biomass-derived polyols obtained from carbohydrates are reduced sugars such as xylitol and sorbitol.[5]

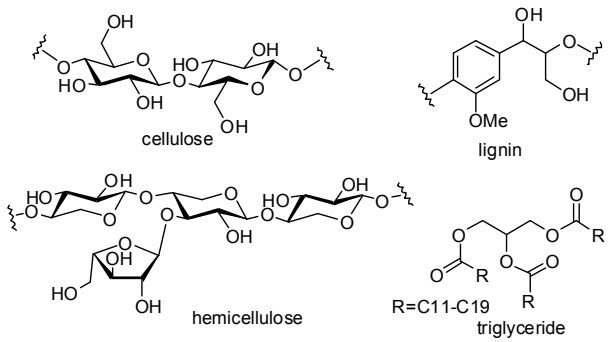


Figure 1. Schematic representation of lignocelluloses (cellulose, hemicellulose, and lignin) and triglycerides structures.

π-Activated alcohols are compounds where the carbon that is bound to the hydroxyl group is adjacent to a carbon–carbon double or triple bond (i.e., allylic, benzylic, and propargylic alcohols) (Figure 2). This unsaturation may activate the hydroxyl group in certain reactions. Glycerol can be converted into an allylic alcohol in one-step and thereby the allylic alcohol can be considered a biomass-derived activated alcohol.[6,7] Benzylic alcohols are found in lignin and can also be considered a biomass source of π-activated alcohols.[8]

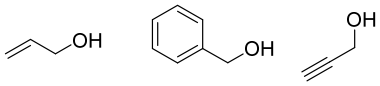
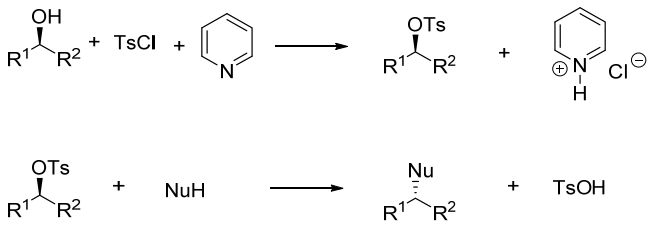


Figure 2. Example of π-activated alcohols

1.2 Traditional nucleophilic substitution of alcohols

A key to use alcohols as starting materials in organic synthesis is to be able to substitute the hydroxyl group with a nucleophile. However, the hydroxyl group is a poor leaving group because the resulting hydroxide ion is a strong base. Therefore, conversion of the hydroxyl group into a better leaving group prior to the nucleophilic substitution is required. The most general method to substitute the hydroxyl group in alcohols is a two-step process. The first step is to convert the hydroxyl group into a tosylate which is a good leaving group. The second step is the substitution of the good leaving group by a nucleophile (Scheme 1). A disadvantage of this method is that both the conversion into the tosylate and also the substitution generates stoichiometric amounts of chemical waste. Another disadvantage is that the intermediate needs purification leading to additional chemical waste.



Scheme 1. Nucleophilic substitution of an alcohol *via* a tosylate.

Another method to substitute the hydroxyl group by a nucleophile is the Mitsunobu reaction. An advantage with this method is that it is a one-step procedure where the hydroxyl group of alcohol is converted *in-situ* to a good leaving group using triphenylphosphine and dialkyl azodicarboxylate such as diethyl azodicarboxylate (DEAD). The nucleophile then attacks the activated alcohol to generate the product. The alcohol undergoes an inversion of configuration under these reaction conditions (Scheme 2). However, this reaction uses the stoichiometric carcinogenic and explosive DEAD and also generates stoichiometric amount of waste, giving rise to tedious purification problems. From safety, environmental, and economical perspectives, these stoichiometric and waste-generating methodologies are not desirable.[9] In this regard, a methodology to activate alcohols for the direct nucleophilic substi-

tution was chosen as the second most desired reaction for pharmaceutical industries. [10]

Scheme 2. Mitsunobu reaction.

In addition, these methods would not be sustainable to use for the conversion of biomass where the hydroxyl group is the most abundant functional group. Instead new sustainable methods that do not produce stoichiometric amount of chemical waste need to be developed. One approach is to use a catalyst to activate the hydroxyl group.

1.3 Catalysis

Catalysis is a process that uses a catalyst to lower the activation energy (Figure 3) and thereby increase the rate of a chemical reaction without consuming of the catalyst during the reaction. Catalysts range from simple acids and bases that promote proton transfers to sophisticated transition metal complexes with chiral ligands that promote asymmetric transformations. In this thesis, palladium based catalysts are used to promote nucleophilic substitution of π-activated alcohols. The elements in group 3 to 12 of the periodic table are commonly called transition metals that have partially filled *d*-orbitals.[11] Many of the transition metal catalysts promote catalysis by their ability to change oxidation state and/or adsorb the reactants to the metal surface and activate them in the catalytic process.

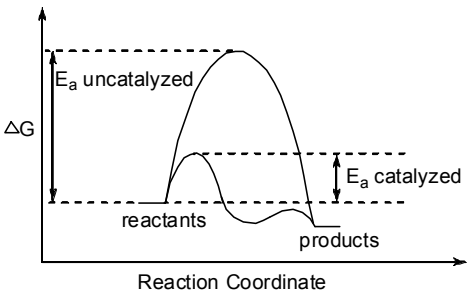
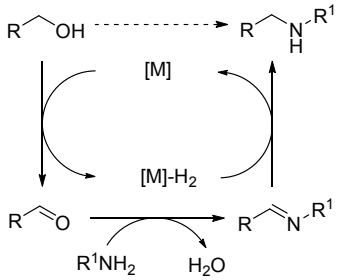


Figure 3. Reaction coordinate diagram for uncatalyzed and catalyzed reactions.

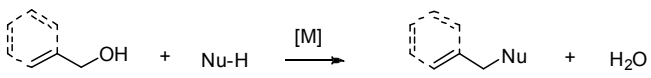
1.4 Modern reactions of alcohols

A recently developed method to substitute alcohols by nucleophiles is the "hydrogen autotransfer" (also named "hydrogen borrowing"). In the hydrogen autotransfer, the transition metal catalyst initially dehydrogenates the alcohol and thereby converts the alcohol into a carbonyl compound (Scheme 3). In contrast to the non-reactive alcohol, the carbonyl intermediate is reactive towards nucleophilic attack. When an amine is used as the nucleophile, a condensation to generate an imine intermediate occurs. The last step of the reaction is when the reduced catalyst MH_2 hydrogenates the imine to generate the amine and regenerate the catalyst.[12] In this process the only side-product is water.



Scheme 3. Hydrogen autotransfer in the alkylation of an amine with an alcohol.

An alternative transition metal-catalyzed reaction to convert alcohols is the direct nucleophilic substitution. There are two different categories of this reaction. In the first category, the transition metal operates as a Lewis acid and coordinates to the oxygen of the hydroxyl group to promote the substitution reaction.[13] In the second category, the transition metal is proposed to perform an insertion into the C–O bond of the hydroxyl group followed by nucleophilic attack. Many different catalysts have been studied for this transformation including: Pd(0),[14] Pd(II),[15] Pt,[16] Ir,[17] , Au,[18] Ru,[19] Cu,[20] Fe,[21] and Zn[22] (Scheme 4). This thesis deals with the latter method in which palladium inserts into the C–O bond of either benzylic or allylic alcohols in the presence of a nucleophile.



Scheme 4. Catalytic nucleophilic substitution of π-activated alcohol.

1.5 Aims of the thesis

The aim of the thesis is to develop efficient methodologies to utilize alcohols as substrates in organic synthesis based on transition metal catalysis. In order to do this, the fundamental steps in the reaction between an alcohol, a catalyst and a nucleophile have been studied. Two model systems were chosen, in which two different palladium-based catalysts cleave the carbon–oxygen bond in π-activated alcohols. The primary objective of the research presented in this thesis has been to increase the understanding of what facilitates the carbon–oxygen bond cleavage of non-manipulated alcohols by palladium-based catalysts. A secondary objective has been to apply the methods to synthetic applications.

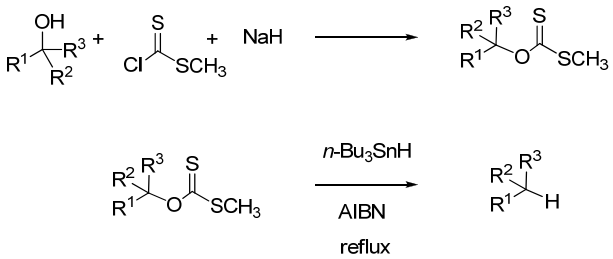
More specific goals are, to increase the understanding of:

- Whether the catalyst cleaves the carbon–oxygen bond of the alcohol or of a more reactive intermediate forming prior to the carbon–oxygen bond cleavage.
- What other species in solution may facilitate the carbon–oxygen bond cleavage.
- The reactive species that is responsible for cleaving the carbon–oxygen bond in alcohols.
- What methods are most suitable to study the reaction mechanism for such transformations.
- Similarities and differences of the carbon–oxygen bond cleaving event between the two different catalytic systems.

2. Pd-Catalyzed Transfer Hydrogenolysis of Benzylic Alcohols (Paper I)

2.1 Background

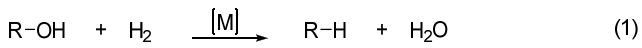
The formal reduction of a C–O bond to the corresponding C–H bond is a fundamental transformation in organic synthesis.[23,24,25] For example, hydrodeoxygenations of hydroxyl groups in sugars have been performed to change the properties of the modified sugar derivatives.[26] Traditionally, either Clemmensen[27] or Wolff-Kishner[28] reductions are performed on ketones or Barton-McCombie deoxygenation[29] is performed on manipulated alcohols (Scheme 5). The formal reduction of a C–O bond to the corresponding C–H bond in benzylic alcohols is usually performed *via* an ester intermediate. Taking into account that benzylic alcohols are abundant functional group in lignin a major component of lignocellulose,[1] efficient methodologies to reduce the C–O bond in benzylic alcohols are highly desired.3,5 A drawback of the traditional methodologies is their use of stoichiometric amount of hazardous reagents. For a sustainable conversion of bulk materials such as lignin, these stoichiometric methodologies are not suitable. Instead, the use of a catalyst and a mild reducing agent would be advantageous.



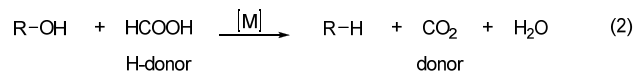
Scheme 5. Barton–McCombie deoxygenation reaction.

An alternative methodology to convert the C–O bond to the corresponding C–H bond is the catalytic hydrogenolysis of alcohols, in which the C–O bond is cleaved and the hydroxyl group is substituted by a hydrogen atom to generate the corresponding alkane and water as the only side-product (Eq 1).2,30 This method has been successfully applied to benzylic alcohols. Most

studies have used catalysts based on palladium on a solid support, *i.e.* carbon.[31,32,33,34] An advantage of using a heterogeneous catalyst is that the catalyst is easily separated from the reaction mixture. A disadvantage with heterogeneous catalyzed reactions is that the mechanism is more challenging to study. It should be noted that indium[35] and rhodium[36] based catalysts have also been reported for the hydrogenolysis reaction of benzylic alcohols. Van Bekkum *et al.* have performed detailed mechanistic studies on the palladium on carbon (Pd/C) catalyzed hydrogenolysis of alcohols in which they demonstrated by isotope labeling that the acidic carbon support facilitates an initial elimination to generate the corresponding styrene that is reduced by a metal-hydride to produce the alkane product.[16] Kwak *et al*. even referred to this as bifunctional catalysis.[37] A disadvantage of using hydrogen gas is over-reduction of the aromatic compounds giving lower chemoselectivity.[38]

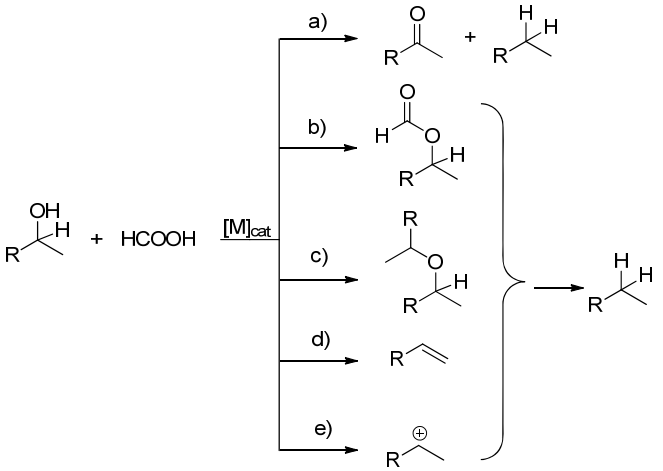


Recently, a hydrogen donor such as an alcohol or formic acid has been used as a hydrogen source and the reaction has been termed as 'transfer hydrogenolysis' (Eq 2).[12,13] In this case, hydrogen gas is transferred from the hydrogen donor, *via* the catalyst, to perform the hydrogenolysis of the alcohol functionality to generate the alkane, water and a donor. In the case of formic acid, carbon dioxide is generated as a donor. Formic acid has many advantages compared with hydrogen gas in regard to its handling, transport, and storage.[39,40] Because carbon dioxide can be recycled into formic acid by hydrogen gas, the overall process is atom efficient[9] and only water is formed as a side-product. Another advantage of using formic acid is that the reaction is more selective towards the hydrogenolysis than the dearomatization giving a reaction with higher chemoselectivity.



While the mechanism of the hydrogenolysis reaction has been thoroughly studied, the corresponding study of transfer hydrogenolysis has not. In fact, no mechanistic studies have been performed, only proposals have been given from experimental observations. When formic acid was used as the hydrogen donor in the Pd/C catalyzed transfer hydrogenolysis of alcohols, a competing disproportionation reaction of the alcohol has been observed (Scheme 6, pathway a). In this case, the alcohol itself acts as both the hydrogen donor and the substrate. A disadvantage with a disproportionation reaction is that only a 50% conversion is possible because the other 50% of the alcohol is lost as reducing agent.[31] Formic acid has also been observed to esterify the alcohol to generate a better leaving group (Scheme 6, pathway b). 6.[41] Other

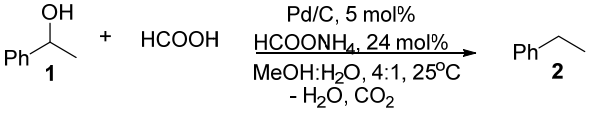
reports indicate that the formate ester intermediate decomposes into the alkane[42] or undergoes elimination to form the alkene.6 The alcohol may also undergo etherification to generate the symmetrical ether in the first step,[43] followed by transfer hydrogenolysis (Scheme 6, pathway c).[44] Formic acid has also been observed to promote an initial elimination to generate the alkene, followed by hydrogenation similar with van Bekkum's study on the catalytic hydrogenolysis of benzylic alcohols (Scheme 6, pathway d).[37] Alternatively, a heterolytic cleavage of C–O bond through a protonation of the hydroxyl group by the formic acid generate a carbenium ion followed by a hydride addition (Scheme 6, pathway e).[31-34] Thereby, the reaction mechanism of the transfer hydrogenolysis of benzylic alcohols, catalyzed by a transition metal has not been sufficiently studied and the reaction mechanism is still not fully understood. In order to develop more efficient catalysts in the future, an increase in the understanding of the elemental steps of the reaction is required.



Scheme 6. Intermediates observed (a-d) and proposed (e) for the transfer hydrogenolysis of alcohols.

2.2 Results and discussion

The importance of developing atom efficient reductions of alcohols for biomass related compounds in particular, in addition to our interest in the mechanism of C–O activation, motivated us to perform a mechanistic study. As a model reaction, (1)-phenylethanol (**1**) was chosen as a model substrate since the reaction is easy to follow and its rate of transfer hydrogenolysis is in a convenient range for kinetic studies (Scheme 7).



Scheme 7. Model reaction for studying transfer hydrogenolysis of **1.**

2.2.1 Nature of the catalyst

To determine the nature of the catalyst, a few experiments were performed. The initial rate of transfer hydrogenolysis of **1** was independent on the stirring rate above 300 rounds per minute (rpm) (Figure 4). This means that above this stirring rate, the reaction is under kinetic and not diffusion control. Also, high reproducibility in the kinetic experiments (relative standard deviation of 3.9%, n = 6) supported that kinetic control, rather than diffusion control, was operating (S.I.).[I]

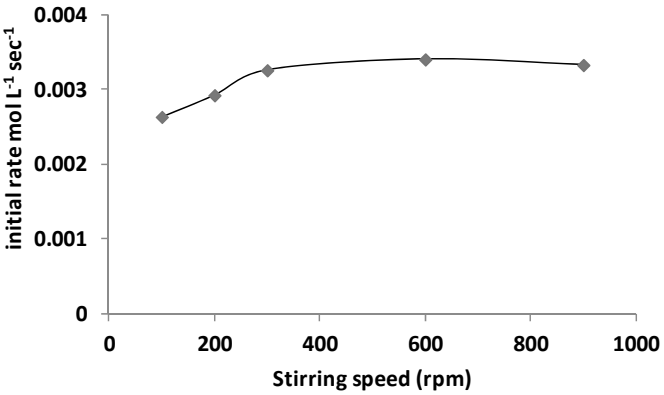


Figure 4. Effect of agitation speeds on initial rate of consumption of **1**. Reaction conditions: **1** (0.4 mmol), Pd/C (4.93 mol%), $HCOONH_4$ (0.095 mmol), HCOOH (1.3 mmol), MeOH (2.4 mL), water (0.6 mL), temperature 25 °C, stirring speed 100-900 rpm.

Poisoning experiments were performed to determine the heterogeneous nature of the catalyst where the addition of triphenylphosphine inhibited the reaction and polymer bound triphenylphosphine did not affect the rate of the reaction (Figure 5).[45] The inhibition experiments supported that the reactive catalyst was indeed a heterogeneous Pd/C catalyst.

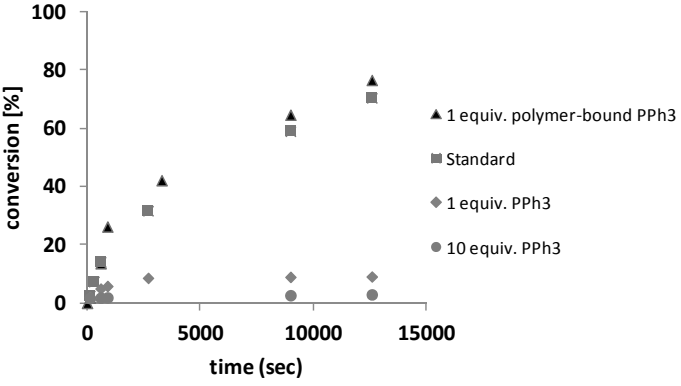
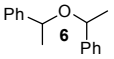


Figure 5. Conversion of **1** as a function of time for the transfer hydrogenolysis under standard conditions. **1** and 10 equiv. of PPh_3 (relative to palladium) were added after 30 sec. 1 equiv. of Polymer-bound PPh_3 (relative to palladium) was added at the beginning of the reaction. Reaction conditions: **1** (0.4 mmol), Pd/C (4.93 mol%), $HCOONH_4$ (0.095 mmol), HCOOH (1.3 mmol), MeOH (2.4 mL), water (0.6 mL), temperature 25 °C, stirring speed 350 rpm.

2.2.2 Initial rates for transformation of postulated intermediates to ethylbenzene

Different intermediates for the catalytic hydrogenolysis and transfer hydrogenolysis of alcohols have previously been proposed (Scheme 6). To exclude some of the previously proposed pathways, reactivity of the resulting intermediates was studied (Table 1). The initial rate of conversion of these possible intermediates were monitored and compared. The observed initial rate for the disappearance of **1** was 3.3×10^{-3} mol $L^{-1}s^{-1}$. Styrene (**3**) underwent a fast transfer hydrogenation with a higher initial rate than **1**. The disappearance of acetophenone **4** also gave a high initial rate. Thereby these two intermediates, especially **3** would be difficult to observe as such during the transfer hydrogenolysis of **1**, and could be regarded as putative reactive intermediates in the catalytic transformation of **1** to **2**. 1-Phenylethyl formate (**5**), the diphenylethyl ether (**6**) and 1-methoxy-1-phenylethane (**7**) were reduced at a lower rate than **1**. Thereby, these species are unlikely to be the intermediates in the catalytic transformation of **1** to **2**.

Table 1. Transfer hydrogenolysis of proposed intermediates.[a]

Entry	Substrate	Initial rate ($\times 10^{-3}$ mol $L^{-1}s^{-1}$)	Entry	Substrate	Initial rate ($\times 10^{-3}$ mol $L^{-1}s^{-1}$)
1	 **1**	3.3	4	 **5**	2.4
2	 **3**	19.1	5	 **6**	0.9
3	 **4**	4.6	6	 **7**	1.2

Conditions: [a] Optimized reaction conditions were used (Substrates (0.4 mmol), Pd/C (4.9 mol%), $HCOONH_4$ (0.095 mmol), HCOOH (1.3 mmol), MeOH (2.4 mL), water (0.6 mL), temperature 25 °C, stirring speed 350 rpm). Initial rate was determined as an average of two runs.

2.2.3 Reaction-order determination

In order to understand the rate-determining step, a reaction-order determination was performed. The reaction-order determination gives an insight into which species are involved in the rate-determining step. Formic acid and formate have been used as hydrogen donors in catalytic transfer hydrogenation and transfer hydrogenolysis reactions.[46] Formate salts have been reported in the transfer hydrogenolysis of benzylic esters and halides, whereas formic acid has been reported for benzylic alcohols. An initial study of the reaction conditions gave interesting results using a combination of formic acid and formate. Using only formate as hydrogen donors for the transfer hydrogenolysis of **1** over Pd/C in a methanol and water mixture at 80 °C, no product was detected. This is probably because the hydroxyl group is a poor leaving group in comparison to esters and halides. Using only formic acid as a hydrogen donor, a disproportionation reaction of **1** afforded a 1:1 ratio of ethylbenzene (**2**) and acetophenone (**4**). After the initial disproportionation, only a very slow transfer hydrogenation to regenerate **1** from **4** was observed. Serendipitously, it was found that catalytic amounts of base and stoichiometric amount of formic acid gave good results which encouraged us to study the effect of the base.[I] The effect of the concentration of ammonium formate on the rate of the reaction was studied (Figure 6). It was found that the rate of the disproportionation reaction is proportionally inhibited by the base (concentrations 0-0.0159 M). Interestingly, even though the rate of the reaction was slower with added base, the reaction went to completion instead

of the 50% conversion to **2**. The rate was independent of the base at concentrations ranging from 0.0159 M to 0.063 M. At these concentrations, negligible concentration of the undesired **4** was observed, and a transfer hydrogenolysis was operating, in which the formic acid acted as a hydrogen donor. Above these concentrations of base, the transfer hydrogenolysis was negatively affected by the base and with only formate, no reaction occurred.

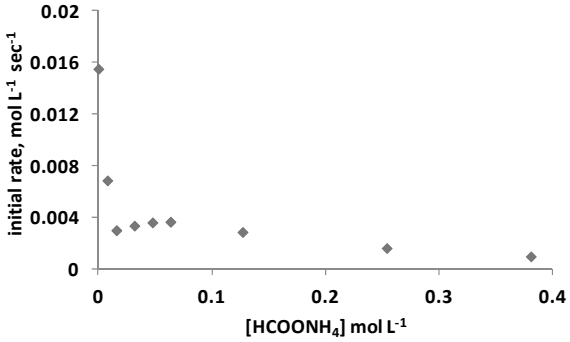


Figure 6. Dependence of the initial rate on concentration of ammonium formate. Reaction conditions: **1** (0.4 mmol), Pd/C (4.9 mol%), $HCOONH_4$ (0.0-0.3806 M), HCOOH (1.3 mmol), MeOH (2.4 mL), water (0.6 mL), temperature 25 °C, stirring speed 350 rpm.

We have already observed that the base has a dramatic influence on the initial rate. However, under the optimized reaction conditions, the effect of the base is negligible in a given concentration window (0.0159-0.063 M). Reaction-order determination was performed on the other species in the reaction mixture. Kinetic studies were performed on the transfer hydrogenolysis of **1** by formic acid catalyzed with Pd/C and ammonium formate at 25 °C. As expected, the initial rate of reaction showed a first-order dependence on the catalyst loading (Figure 7).

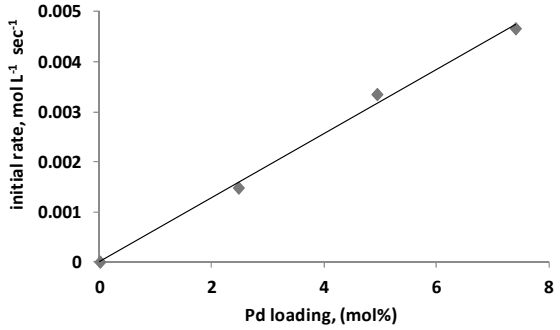


Figure 7. Dependence of initial rate on catalyst loading in the Pd/C catalyzed transfer hydrogenolysis of **1** by formic acid. Reaction conditions: **1** (0.4 mmol), Pd/C (2.47−7.40 mol %), $HCOONH_4$ (0.095 mmol), HCOOH (1.3 mmol), MeOH (2.4 mL), water (0.6 mL), temperature 25 °C, stirring speed 350 rpm.

The concentration of **1** was varied 0.06-2.6 M, and initial rates were determined at a conversion of **1** below 10%. The initial rate of the reaction was independent of the alcohol concentration (Figure 8). This result indicates that the C–O bond cleavage is not involved in the rate-determining step.

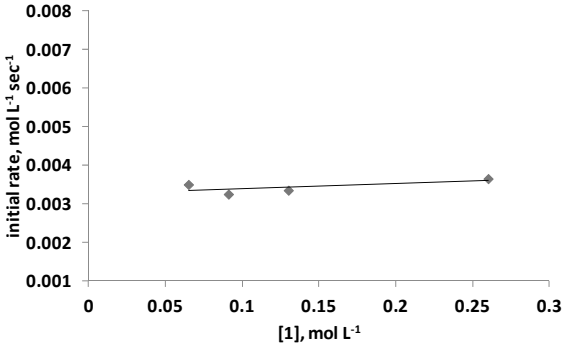


Figure 8. Dependence of initial rate on concentration of substrate **1** in the Pd/C catalyzed transfer hydrogenolysis of **1** by formic acid. Reaction conditions: **1** (0.065-0.26 M), Pd/C (4.9 mol%), $HCOONH_4$ (0.095 mmol), HCOOH (1.3 mmol), MeOH (2.4 mL), water (0.6 mL), temperature 25 °C, stirring speed 350 rpm.

The plot of the initial rate of reaction *versus* the concentration of hydrogen donor is shown in Figure 9. The initial rate of the reaction showed a first-order dependence on the concentration of formic acid. These results support a reaction mechanism in which the proton and/or hydride transfer between formic acid and Pd/C is involved in, or precedes, the rate-determining step.

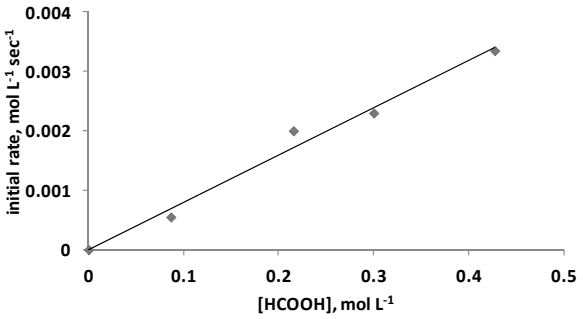


Figure 9. Dependence of the initial rate on concentration of formic acid in the Pd/C catalyzed transfer hydrogenolysis of **1** by formic acid. Reaction conditions: **1** (0.4 mmol), Pd/C (4.9 mol%), $HCOONH_4$ (0.095 mmol), HCOOH (0.087-0.427 M), MeOH (2.4 mL), water (0.6 mL), temperature 25 °C, stirring speed 350 rpm.

The data set is in agreement with an overall second-order reaction that is first-order dependent on both Pd/C and formic acid (Eq 3). It should be noted that this applies to the transfer hydrogenolysis reaction at 0.0159-0.063 M base concentrations. At lower concentrations of the base, a fast disproportionation reaction occurs giving the desired product in 50% yield. At higher concentrations of the base, the transfer hydrogenolysis is inhibited.

$$-\frac{d[\mathbf{1}]}{dt} = k\,[\mathrm{Pd}][\mathrm{HCOOH}] \qquad (3)$$

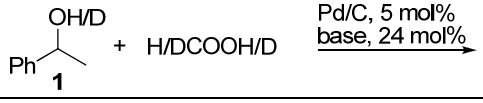
The rate equation implies that the hydrogen transfer between the formic acid and Pd/C is involved in the rate-determining step, and that C–O bond cleavage is not. We decided to study the hydrogen transfer in detail to determine whether the proton and/or the hydride transfer occur in the rate-determining step. A way to study the hydrogen transfer is to replace hydrogen by deuterium and measure how this exchange affects the rate of the reaction.

2.2.4 Deuterium kinetic isotope effects

Various deuterium-labeled formic acids (DCOOH, HCOOD, and DCOOD) were used to determine the relative rates of C–H and O–H bond cleavages for hydrogen transfer from the formic acid to palladium. Comparing the initial rates of the reactions with deuterium-labeled formic acids, a primary kinetic isotope effect (KIE) of 2.26 was observed when deuterium in the hydridic position was used (DCOOH). An inverse kinetic isotope effect of 0.6 was observed for the proton transfer (HCOOD). A combined kinetic isotope effect of 1.41 was observed when formic acid with deuterium in both hydridic and protic positions (DCOOD) was used (Table 2). Interestingly

this is in agreement with the product of the two individual isotope effects ($0.62 \times 2.26 = 1.40$). The latter implies that both the proton and hydride may be transferred simultaneously from formic acid to Pd/C in a concerted mechanism.

Table 2. Deuterium kinetic isotope effects for transfer hydrogenolysis of **1**.

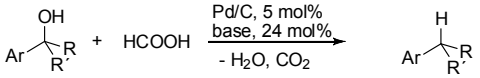


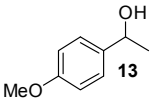
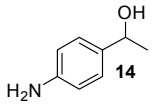
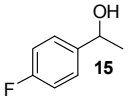
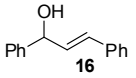
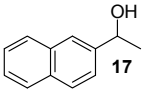
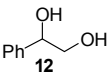
k_{CHOH} / k_{CDOH}	2.26 ± 0.24
k_{CHOH} / k_{CHOD}	0.62 ± 0.06
k_{CHOH} / k_{CDOD}	1.41 ± 0.11

2.3 Substrate scope

Under the optimized reaction conditions, (a 5:1 ratio of base to Pd/C, 3 equiv. of formic acid, methanol and water, 80 °C),[I] the transfer hydrogenolysis of a variety of benzylic alcohols generated the corresponding aromatic hydrocarbons in moderate to excellent yields (56-99% yields) as shown in Table 3. 1-Phenylethane-1,2-diol (**12**) was selectively reduced in the benzylic position to generate a corresponding aromatic hydrocarbon in 56% conversion (Table 3, entry 6). These substrates demonstrate a broad scope in which primary, secondary, and tertiary benzylic alcohols were reduced to their corresponding hydrocarbons.

Table 3. Pd-catalyzed transfer hydrogenolysis of different benzylic alcohols.[a]



Entry	Substrate	Yield[b](%)	Entry	Substrate	Yield[b](%)
1	 **1**	98	7	 **13**	98
2	 **8**	87	8	 **14**	96
3	 **9**	61	9	 **15**	50[d]
4	 **10**	95[c]	10	 **16**	67[c]
5	 **11**	94[c]	11	 **17**	78
6	 **12**	56[c,d]	12	 **18**	99[c]

Conditions: [a] Alcohol (0.4 mmol), 5% Pd/C (42 mg), $HCOONH_4$ (0.095 mmol), HCOOH (1.3 mmol), MeOH (2.4 mL), water (0.6 mL), temperature 80 °C, 40 min. [b] Yields was calculated using ^1H NMR with mesitylene as an internal standard. [c] Isolated yield. [d]10 mol% of Pd was used.

2.4 Mechanistic discussion

Scheme 6 in the introduction depicts the intermediates of some possible pathways for the Pd/C catalyzed transfer hydrogenolysis of benzylic alcohols by formic acid. As discussed below, the experimental results provide a reason to exclude these mechanistic proposals. Finally, a new reaction mechanism is proposed and discussed.

Disproportionation and transfer hydrogenation pathway: The observation that the rate of reaction of **4** is higher than that of **1** leading to **4** not being observed in the reaction media is in accordance with this reaction mechanism (Scheme 8, Path A). However, there are two observations that are difficult to explain if the reaction would proceed through this reaction mechanism. First, the transfer hydrogenolysis was successful even with ter-

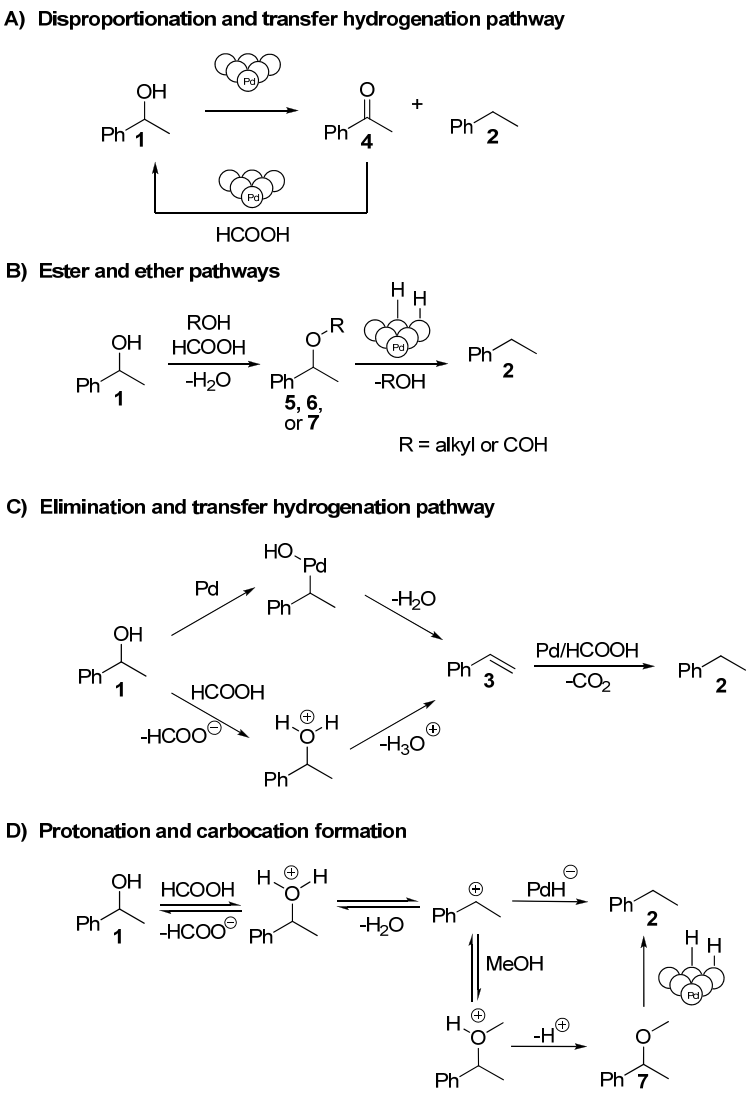
tiary alcohols (Table 3, entries 2, 4, 12) which cannot undergo β-hydride elimination. Second, the initial rate was independent of **1** is inconsistent with a disproportionation pathway, where a rate-determining transfer dehydrogenation is expected to be operating during the initial turnovers.

Ester and ether pathways: Both ester and ether pathways have been postulated by other research groups (Scheme 6). Since the rate of transfer hydrogenolysis of both the ester and ethers were much slower than that of **1** (Table 1), one would expect these intermediates to be detectable by ^{1}H NMR spectroscopy if they were present. However, compounds **5-7** (Table 1) were not detected in any of our ^{1}H NMR spectra under the reaction conditions.

Elimination and transfer hydrogenation pathway: An elimination *via* an acid-catalyzed E_1-mechanism or by a Pd/C insertion of the C–O bond, followed by a β-hydride elimination has been suggested as the pathway for the hydrogenolysis of alcohols by hydrogen gas (Scheme 6, Path D). The acid-catalyzed elimination reaction would generate styrene in the absence of palladium, but this was not observed in subsequent studies (Scheme 8, Path C). Moreover, if this was the case, tertiary benzylic alcohols would be expected to undergo faster transfer hydrogenolysis than secondary benzylic alcohols, but this was not observed. Furthermore, substrates (examples with primary, secondary, and tertiary benzylic alcohols are given in Table 3) where no elimination was possible were successfully transformed to the corresponding hydrocarbons.

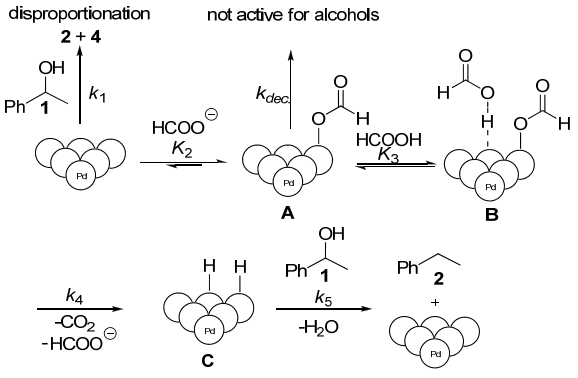
Protonation and carbocation formation: The formic acid may facilitate protonation to convert the hydroxyl group of **1** into a better leaving group, and subsequently eliminated to generate a carbenium ion (Scheme 8, Path D). There are a few observations that support this mechanistic pathway: *para*-substitution by electron-donating substituents facilitated transfer hydrogenolysis, while electron-withdrawing substituents slow down the reaction (Table 3, entries 7-9). The primary benzylic alcohols showed lower reactivity than the secondary and tertiary benzylic alcohols (Table 3, entries 1-3). However, there are a few observations that are difficult to explain with this mechanism: If the carbenium ion was generated, the excess methanol in the reaction medium is expected to trap the carbenium ion and form 1-methoxy-1-phenylethane (**7**), *via* an S_N1 mechanism. If the ether was an intermediate in the reaction, it would have been observed because the rate of reduction of the ether is lower than that of **1**, and it was not. Furthermore, the reaction rate for a tertiary benzylic alcohol would be expected to be faster than a secondary benzylic alcohol if the reaction proceeded through a carbenium ion intermediate. Primary benzylic alcohols, highly unlikely to generate a carbenium ion also worked in the present reaction and this would not be expected.

Scheme 8. The proposed mechanisms of transfer hydrogenolysis.



None of the postulated reaction mechanisms can explain all of the afore mentioned data including the substrate scope, reactivity of proposed intermediates, the effect of the base, the rate order, and the deuterium kinetic isotope effect, thus a novel mechanism is considered.

Proposed mechanism: As shown in Figure 6, the base plays an important role for a facile transfer hydrogenolysis reaction. In the mechanistic proposal, a formate anion adsorbs to palladium, forming formato-palladium intermediate **A** (Scheme 9). This inhibits the surface of palladium for the alcohol and thereby the disproportionation pathway ($K_2 > k_1$). This is in accordance to the negative rate dependence for the base between 0 to 0.016 M (Figure 6), where the mechanism changes from a fast disproportionation to a slower transfer hydrogenolysis. The equilibrium of complexes **A** and **B** in the presence of formic acid is consistent with the inverse kinetic isotope effect for the proton transfer ($k_{CHOH}/k_{CHOD} = 0.62 \pm 0.06$). A decomposition of complex **B** to palladium hydrogen species (**C**) in a rate-determining step is consistent with the primary kinetic isotope effect for the hydride transfer ($k_{CHOH}/k_{CDOH} = 2.26 \pm 0.24$).[30,47,48] The proton and the hydride may be transferred from formic acid to palladium in a concerted process. This is in agreement with the product of the two individual isotope effects ($0.62 \times 2.26 = 1.40$), is within experimental error of the combined D isotope effect measured ($k_{CHOH}/k_{CDOD} = 1.41 \pm 0.11$), in accordance to Casey's methodology to determine concerted hydrogen transfers in transition metal catalysis.[49] Complex **C** reduces the benzylic alcohol in a rapid step.[50] The rate of the reaction was independent of the concentration of benzylic alcohol, consistent with a mechanism in which the C–O bond cleavage is not involved in the rate-determining step.



Scheme 9. Proposed reaction mechanism of the transfer hydrogenolysis of **1** by formic acid.

2.5 Conclusions

The Pd/C-catalyzed transfer hydrogenolysis of benzylic alcohols by formic acid is only possible in the presence of a catalytic amount of base, where the rapid disproportionation reaction is inhibited. The role of the base is to inhibit the disproportionation pathway by occlusion of vacant coordination sites on Pd.

Under these reaction conditions, secondary and tertiary alcohols underwent the reaction to afford the corresponding aromatic hydrocarbons in excellent yields whereas primary benzylic alcohols gave moderate yields.

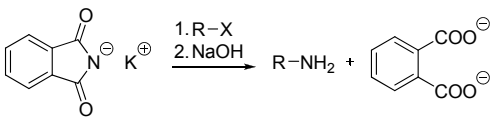
Inhibition experiments and kinetic experiments show that the heterogeneous Pd/C and not leaked colloidal metal is responsible for the transfer hydrogenolysis reaction. Mechanistic studies have been performed. Surprisingly, the C–O bond cleavage does not occur in the rate-determining step, determined by a zero-order dependence of the benzylic alcohol. Instead the hydride transfer from formic acid to palladium is involved in the rate-determining step, determined by kinetic isotope effect.

A reaction mechanism for the Pd/C catalyzed transfer hydrogenolysis of benzylic alcohols by formic acid has been proposed. The charged formate anion coordinates to the surface of Pd/C more efficiently than the benzylic alcohol. This coordination by the formato anion is responsible for changing the reactivity from a rapid disproportionation reaction to a slower transfer hydrogenolysis reaction. This formato palladium complex is not reactive in the transfer hydrogenolysis of benzylic alcohols. In the presence of formic acid, the formato-palladium complex equilibrates rapidly with a proton from formic acid to give complex **B**. Complex **B** decomposes into the reactive palladium-hydrogen species in a rate-determining step. The proton and hydride transfer from formic acid to palladium may occur in a concerted step to generate palladium dihydride species. The dihydride species is responsible for the cleavage of the C–O bond of the benzylic alcohol. This dihydride species may resemble the dihydride species in the disproportionation reaction. It is noteworthy that the C–O bond cleavage does not occur in a rate-determining step.

3. Palladium-Catalyzed Amination of Allylic Alcohols (Papers II, III, IV)

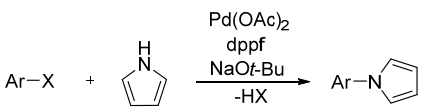
3.1 Background

The formation of a C–N bond is a fundamental reaction in organic synthesis. The amine functionality is found in naturally abundant substances and also in a large number of pharmaceuticals.[51] Traditionally, amines are prepared by a number of different reactions *e.g.* Gabriel synthesis (Scheme 10),[52] Curtius rearrangement[53] and reductive amination.[54] These methodologies make use of stoichiometric amount of reagents and generate stoichiometric amount of waste. In many cases hazardous chemicals are used as starting material or produced as a byproduct. Due to the importance of these compounds, a catalytic procedure that generates less waste would be desirable.



Scheme 10. Gabriel synthesis of amines.

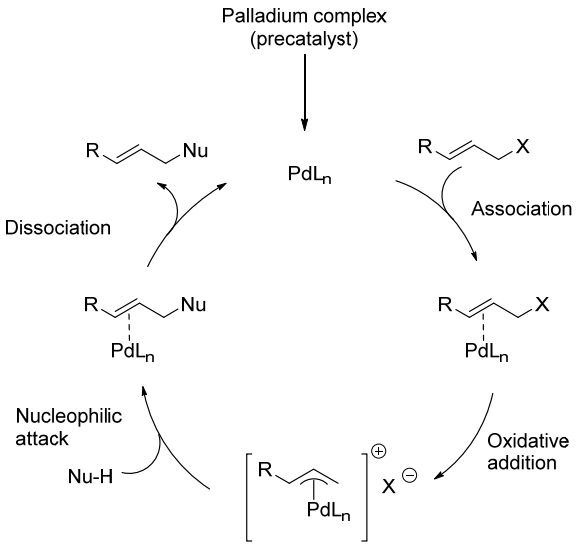
In Chapter 1, the "Hydrogen autotransfer reaction" as an example of a catalytic C–N bond forming reaction was introduced. Another example of a catalytic reaction that forms a C–N bond is the Buchwald-Hartwig coupling in which an aryl halide and amine react in the presence of a stoichiometric amount of base (Scheme 11).[55]



Scheme 11. Buchwald-Hartwig coupling.

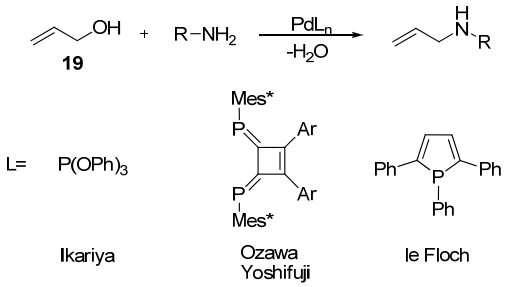
A further example of a catalytic reaction which generates a C–N bond is the Tsuji-Trost reaction.[56] The Tsuji-Trost reaction is defined as a palladium-catalyzed allylic substitution of nucleophiles with allylic compounds. The

reaction is considered to proceed *via* the formation of the π-allylpalladium intermediates (Scheme 12). The general accepted mechanism for the catalytic cycle of the reaction starts with coordination of the palladium(0) complex to the double bond of the allylic substrate, followed by an oxidative addition to form the π-allylpalladium complex. Nucleophilic attack to the terminal carbon of the π-allyl affords an η^2-complex with the product coordinated to palladium. Dissociation of the product regenerates the active catalyst.



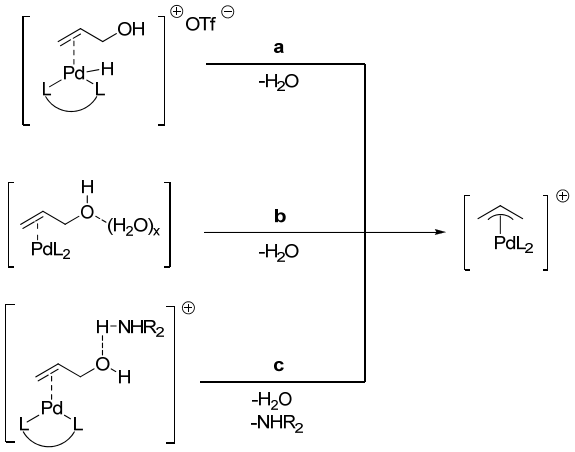
Scheme 12. General catalytic cycle of Tsuji-Trost reaction.

The Tsuji-Trost reaction has been carried out using palladium and various allylic sources such as halides[57a], esters,[57b,57c] ethers,[57d] and carbonates.[57e] Palladium-catalyzed direct amination of allylic alcohols has recently attracted attention due to economic and environmental advantages but a limited numbers of conversions of unactivated allylic alcohol into π-allylpalladium intermediate has been reported in the literature. Because it is difficult to cleave the C–O bond of an alcohol due to the hydroxyl group's poor leaving group ability, the palladium-catalyzed direct substitution of allylic alcohol (**19**) usually requires activation by a Lewis acid.[58] Recently, palladium complexes bearing strong π-acceptor ligands (phospholes,[59] diphosphinidenecyclobutene[15a] and triphenylphosphite[14a]) have been reported to achieve this transformation without the use of activators (Scheme 13).



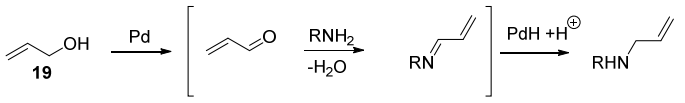
Scheme 13. Palladium-catalyzed amination with allylic alcohol.

A key step in the direct amination of allylic alcohol **19** is the C–O bond cleavage of the hydroxyl group to form a π-allylpalladium intermediate. Different pathways have been proposed as shown in Scheme 14. Ozawa proposed that a hydridopalladium complex bearing the diphosphinidenecyclobutene ligand was responsible for this process (path a).[15a] Theoretical calculations have supported a water assisted hydrogen bonding to activate hydroxyl group to generate π-allylpalladium intermediate (path b)[60] or alternatively an allylammonium salt activates the hydroxyl group (path c).[61]



Scheme 14. Proposed mechanism for the C–O bond cleavage of the hydroxyl group of allylic alcohol.

The allylation of aniline from unactivated allylic alcohols can also proceed by hydrogen autotransfer mechanism to generate butenal, followed by condensation of aniline and finally palladium hydride insertion gives the final product (Scheme 15).[62]



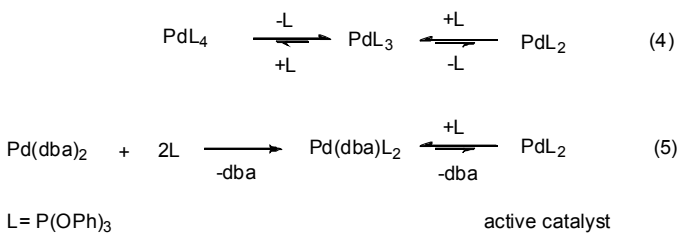
Scheme 15. Hydrogen borrowing or hydrogen autotransfer mechanisms.

Still, the reaction mechanism of the C–O bond cleavage in the Tsuji-Trost reaction of **19** is not understood. In order to develop more efficient catalysts in the future, a better understanding of the elemental steps of both the C–O bond activation and also the C–N bond forming step is required.

3.2 Results and discussion

3.2.1 Nature of the catalyst

According to the literature, $Pd[P(OPh)_3]_4$ can be generated either from $PdCl_2(MeCN)_2$ in the presence of NEt_3 and $P(OPh)_3$ or *in-situ* from $Pd(dba)_2$ and $P(OPh)_3$ in a 1:4 molar ratio. The latter procedure is convenient to use in catalysis for practical reasons. We initially observed that increasing the ratio between $Pd(dba)_2$ and $P(OPh)_3$ above 1:4 had a small influence on the reactivity. Jutand and Amatore have thoroughly studied the equilibrium of phosphines and $Pd(dba)_2$ and found that the dba ligand is not as innocent as expected. To our knowledge the corresponding study on triarylphosphite ligands and $Pd(dba)_2$ has not been reported. Furthermore, there is a possibility that either $Pd[P(OPh)_3]_4$ (Eq 4) or $Pd(dba)[P(OPh)_3]_2$ (Eq 5) can operate as catalyst precursor to generate the reactive species $Pd[P(OPh)_3]_2$ that is believed to be the active catalyst in the allylation reaction of aniline by allylic alcohol. This motivated us to study the equilibrium between $Pd(dba)_2$ and $P(OPh)_3$.



Both $Pd[P(OPh)_3]_3$ and $Pd(dba)[P(OPh)_3]_2$ complexes were synthesized and isolated. The complexes were crystallized and elucidated by X-ray crystal-

lography. An interesting feature of the proposed $Pd[P(OPh)_3]_4$ complex is that there are 3 ligands and not 4 coordinated to palladium in the planar $Pd[P(OPh)_3]_3$ complex. The ^{31}P NMR spectrum of $Pd[P(OPh)_3]_3$ shows one signal at 138.8 ppm (Figure 10b) which is characteristic of palladium bearing three triphenylphosphite ligands which are identical as shown in Figure 10g. The ^{31}P NMR spectrum of $Pd(dba)[P(OPh)_3]_2$ shows two broad signals ($\Delta\nu_{1/2}$= 61 Hz) of equal magnitude at 137.6 and 133.4 ppm. As expected, two phosphorus atoms of $Pd(dba)[P(OPh)_3]_2$ are crystallographically nonequivalent (Figure 10h), thus the ^{31}P NMR spectrum exhibits two broad signals. This complex also exhibits a planar coordination.

The ^{31}P NMR spectrum of a mixture of $Pd(dba)_2$ with 2 equiv. of $P(OPh)_3$ reveals three signals (Figure 10d): one signal at 138.8 ppm (Figure 10b) is characteristic of $Pd[P(OPh)_3]_3$ and two broad signals ($\Delta\nu_{1/2}$= 61 Hz) of equal magnitude at 137.6 and 133.4 ppm which establish $Pd(dba)[P(OPh)_3]_2$, as shown in Figure 10c. Upon addition of 4 and 8 equiv. of $P(OPh)_3$ to $Pd(dba)_2$ one broad signal at 135.5 and δ 130.8 ppm was revealed. The broad signal indicates palladium (0) complexes in equilibrium with the $P(OPh)_3$.

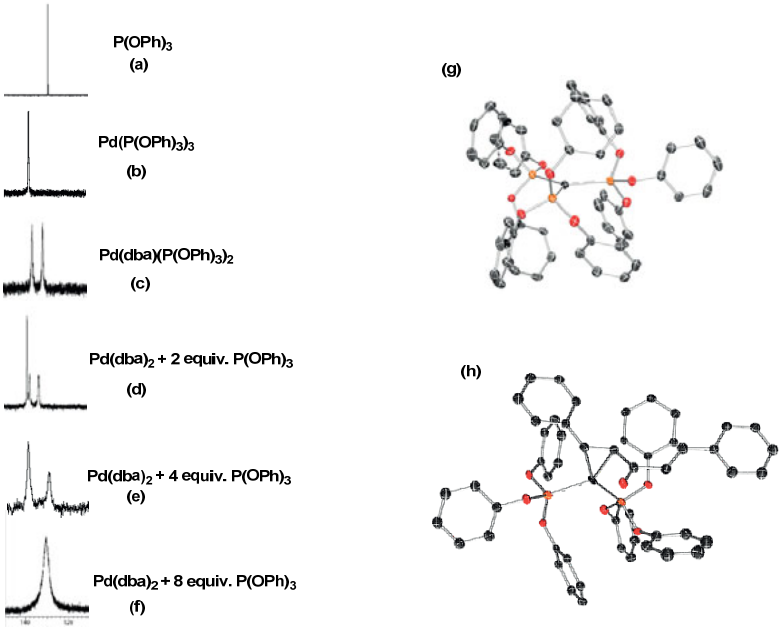


Figure 10. $^{31}P\{^1H\}$ NMR spectra (121 MHz) performed in 0.6 mL of benzene-d_6 with H_3PO_4 as an external standard: (a) $P(OPh)_3$ (b) $Pd[P(OPh)_3]_3$, (c) $Pd(dba)[P(OPh)_3]_2$, (d) $Pd(dba)_2$ (15 mM) + $P(OPh)_3$ (30 mM), (e) $Pd(dba)_2$ (15 mM) + $P(OPh)_3$ (60 mM), (f) $Pd(dba)_2$ (15 mM) + $P(OPh)_3$ (120 mM), (g) X-ray crystal structure of $Pd[P(OPh)_3]_3$, (h) X-ray crystal structure of $Pd(dba)[P(OPh)_3]_2$.

The broadened signals observed at a 1:4 ratio between $Pd(dba)_2$ and $P(OPh)_3$, can have different explanations. Therefore, we decided to investigate this by cooling down the probe and study the temperature effect of the equilibrium by ^{31}P NMR spectroscopy. At -20 °C the two broad signals separated to give two new chemical shifts at 127.2 and 138.5 ppm (Figure 11). The ratio of the integral between the chemical shifts changed from 7:3 (at 25 °C in favor of the signal at 138.5 ppm) to 1:1 at -20 °C. At -40 °C the signal at 127.2 ppm split into two new signals at 126.1 and 127.1 ppm. The ratio between the three signals at 126.1, 127.1, and 139.2 ppm was 1:2:1. At -60 °C the signals separated further to give new signals at 125.4, 127.4, and 139.4 ppm. The ratio between these signals was integrated to 4:13:1. We propose that the signal at 127.4 ppm (-60 °C) corresponds to the $Pd[P(OPh)_3]_4$ complex. At higher temperatures, this complex is in an equilibrium with $Pd[P(OPh)_3]_3$ and $P(OPh)_3$ giving rise to a broadened signal. At low temperatures, the tetracoordinated complex is more stable than the $Pd[P(OPh)_3]_3$ complex.

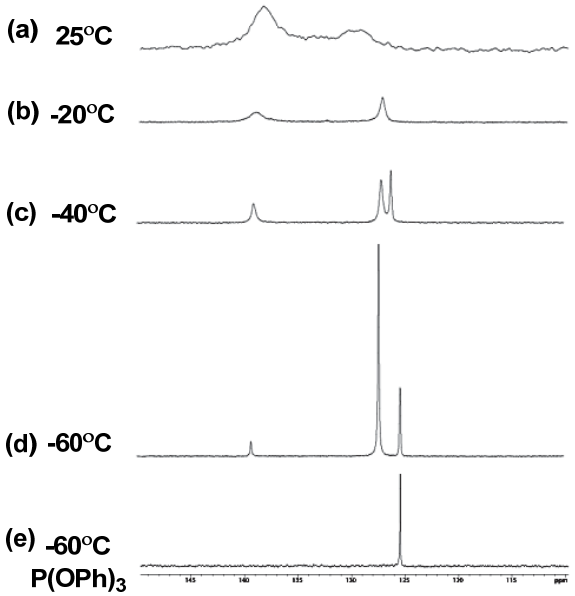


Figure 11. VT-$^{31}P\{^1H\}$ NMR spectra (121 MHz) performed in 0.6 mL of tolunene-d_8, $Pd(dba)_2$ (15mM) + $P(OPh)_3$ (60mM) with H_3PO_4 as an external standard at temperatures between 25 °C and -60 °C.

Both isolated complexes were evaluated in the allylation reaction of aniline (**20a**) by **19** (Figure 12). The measurements of the catalytic activity of pure $Pd(dba)[P(OPh)_3]_2$ and $Pd[P(OPh)_3]_3$ showed that the $Pd(dba)[P(OPh)_3]_2$ complex had a 70% lower reactivity than the $Pd[P(OPh)_3]_3$ complex. This suggests that a rapid equilibrium of the $Pd(dba)[P(OPh)_3]_2$ complex and $Pd[P(OPh)_3]_3$ was operating, and would correspond to the equilibrium study where the observed ratio; $Pd(dba)[P(OPh)_3]_2$ and $Pd[P(OPh)_3]_3$, was 1:3 at a $Pd(dba)_2$:$P(OPh)_3$ ratio of 1:2. Thereby, the reactivity of $Pd(dba)[P(OPh)_3]_2$ (70% of the reactivity for pure $Pd[P(OPh)_3]_3$) was within experimental error of what was expected for the actual concentration of $Pd[P(OPh)_3]_3$ (75%) at a $Pd(dba)_2$:$P(OPh)_3$ ratio of 1:2.

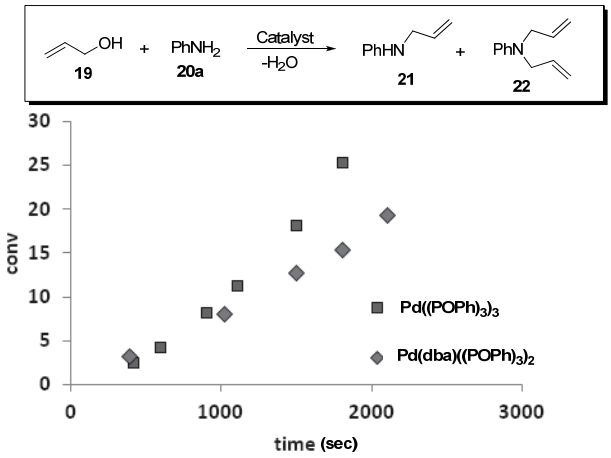


Figure 12. $Pd(dba)[P(OPh)_3]_2$ and $Pd[P(OPh)_3]_3$ complexes in the allylation of **20a** by **19**. Reaction conditions: **19** (0.840 M), **20a** (0.209 M), Pd catalyst (2 mol%), benzene-d_6, 60 °C.

3.2.2 Reaction-order determination

In order to understand the rate-determining step, a reaction-order determination was performed. The reaction-order determination gives an insight into which species are involved in the rate-determining step. We had already observed that the reaction proceeded faster with an excess of allylic alcohol (**19**).

The rate of allylation of aniline (**20a**) with allylic alcohol (**19**) was observed by using ^{1}H NMR spectroscopy to monitor the appearance of product in benzene-d_6. As expected, the initial rate of the allylation of **20a** by **19** shows a first-order dependence on $Pd[P(OPh)_3]_3$ concentration. Interestingly, the rate of the reaction is independent of **20a** and also water concentrations.

Thereby, neither ammonium salt nor water are involved in the rate-determining step of the $Pd[P(OPh)_3]_3$ catalyzed allylic amination.[58,61] Thereby, the theoretical proposals in Scheme 14 cannot be supported by these experiments. Surprisingly, the allylation of **20a** from **19** catalyzed by $Pd[P(OPh)_3]_3$ showed second-order dependence on **19** concentration (Figure 13).

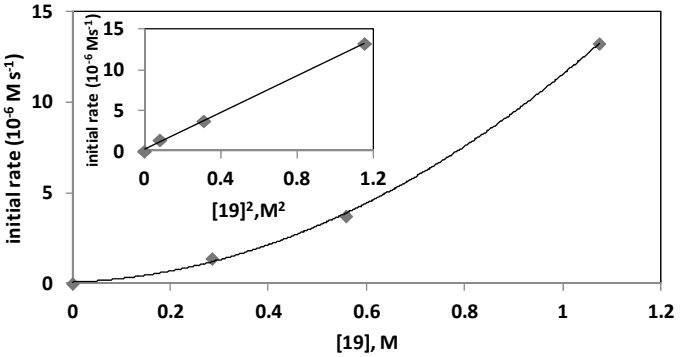


Figure 13. Second-order dependence of the initial rate on the concentration of **19** in the $Pd[P(OPh)_3]_3$ catalyzed the allylation of **20a**. Reaction conditions: substrate **19** (0.174-0.696 M), **20a** (0.174 M), $Pd[P(OPh)_3]_3$ (2 mol %), benzene-d_6, 55 °C.

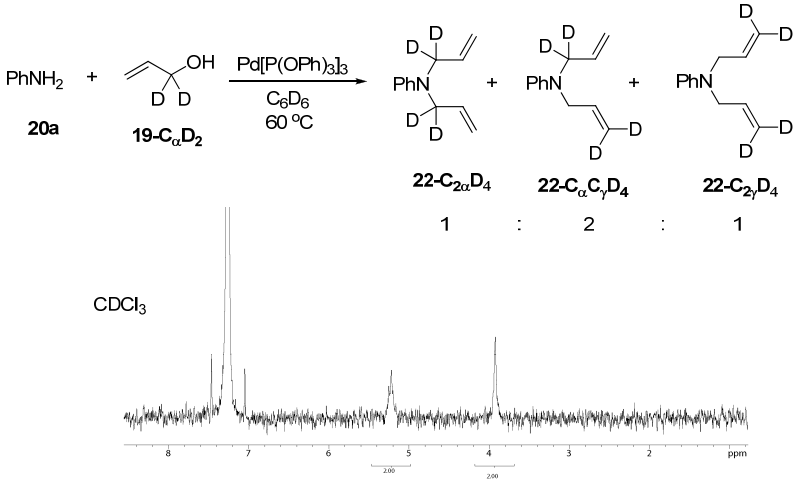
Thereby, a rate equation for the allylation of **20a** from **19** catalyzed by $Pd[P(OPh)_3]_3$ under standard conditions can be expressed as in equation 6. The second order rate-dependence in **19** could be explained by a hydrogen bonding assistance promoted by **19** in analogy to what has previously been proposed for water or ammonium (Scheme 14, paths b and c). Alternatively, the role of the second molecule of **19** is to act as a hydrogen source to generate a palladium hydride intermediate (Scheme 14, path a). A way to study this is to label the allylic alcohol (**19**) at different positions by deuterium and study the kinetic isotope effects.

$$\text{rate} = k[Pd][\mathbf{19}]^2 \qquad (6)$$

3.2.3 Deuterium kinetic isotope effects and isotope labeling

Synthesis of allyl-1,1-d_2 alcohol (**19-$C_\alpha D_2$**) was performed. With this compound in hand, we could easily determine whether the reaction proceed through a hydrogen autotransfer mechanism or *via* π-allylpalladium intermediate. If the reaction proceeded through a hydrogen autotransfer mechanism, deuterium would only show up vicinal to nitrogen and if the reaction proceeded through a π-allylpalladium intermediate, scrambling of the deuterium

between vicinal and terminal positions is expected. Allylation of aniline by allyl-1,1-d_2 alcohol proceeded to generate the 1:2:1 mixture of the diallylated aniline in which the total deuterium content was evenly distributed to α- and γ-positions of the diallylated amines (Scheme 16). The statistical outcome where the deuterium was observed in both the α- and γ-positions is consistent with a mechanism involving a π-allylpalladium intermediate.



Scheme 16. Amination of deuterated allylic alcohol gives a statistical distribution of products as expected for a mechanism involving a π-allylpalladium intermediate and ^{2}H NMR spectrum of the isolated products.

Considering an unprecedented second-order dependence on allylic alcohol (**19**) concentration, deuterium kinetic isotope effect (KIE) measurements for the allylation of **20a** by **19** were conducted to gain an insight into the mechanism of this transformation. A large secondary deuterium KIEs (k_{CH}/k_{CD} = 1.34 ± 0.01) was observed (Table 4) when comparing the initial rates of allylation of aniline by **19-$C_\alpha D_2$** and **19**. For comparison, we carried out additional deuterium KIE experiments with allyl benzoate (**23)** having a good leaving group. A secondary KIEs for allyl benzoate (k_{CH}/k_{CD} = 1.11 ± 0.04) was determined by preparing allyl 1,1-d_2 benzoate (**23-$C_\alpha D_2$**) and comparing its rate of allylation to **23** at 25 °C.[63] The use of CH_2=$CHCH_2OD$ (**19-OD**) for the allylation of **20a** with $Pd[P(OPh)_3]_3$ gave a primary deuterium KIEs (k_{OH}/k_{OD} = 2.06 ± 0.08) indicating that an O–H bond cleavage occurs either before or in the rate-determining step (Table 4). To determine whether the cleavage of the O–H bond proceeds before, simultaneously, or after the C–O bond cleavage, the allylation of **20a** was carried out with doubly labeled CH_2=$CHCD_2OD$ (**19-$C_\alpha D_2$OD)**. Comparison of the rate constants for the reaction of amination with **19** and **19-$C_\alpha D_2$OD** gave deuterium KIEs of (k_{CHOH}/k_{CDOD} = 2.05 ± 0.02) (Table 4). Thereby, the doubly labeled

allylic alcohol (**19-$C_\alpha D_2$OD**) showed a similar KIE (2.05) as observed for **19-OD** (2.06).[64]

Table 4. Deuterium kinetic isotope effects on the allylation of **20a** with **19** or **23** by $Pd[P(OPh)_3]_3$.

19/19-$C_\alpha D_2$	k_{CH}/k_{CD}	1.34 ± 0.01
19/19-OD	k_{OH}/k_{OD}	2.05 ± 0.02
19/19-$C_\alpha D_2$OD	k_{CHOH}/k_{CDOD}	2.06 ± 0.08
19-OD/19-$C_\alpha D_2$OD	k_{CDOH}/k_{CDOD}	1.00 ± 0.05
23/23-$C_\alpha D_2$	k_{CH}/k_{CD}	1.11 ± 0.04

The absence of a product isotope effect rules out the possibility that the role of the second molecule of **19** is to activate the hydroxyl group of **19,** which is similar to what has been proposed for water or ammonium ion (Scheme 14, paths b and c). If the two steps would occur simultaneously, the product of the primary and secondary isotope effects would be expected.[I,49a]The results are consistent with a mechanism in which the O–H bond cleavage occurs in a separate step, prior to the C–O bond cleavage, with either negligibly lower or similar activation energy (Figure 14). This would explain why the secondary KIE is not observed in the presence of the primary KIE.[65] These data are also consistent with the observed second-order dependence in **19**. Thus, the primary deuterium KIE of 2.06, may indeed indicate an insertion by palladium to the O–H bond of **19** to generate a palladium hydride intermediate in the rate-determining step.
The intermediacy of a palladium hydride intermediate was also supported by ESI-MS experiments.[III]

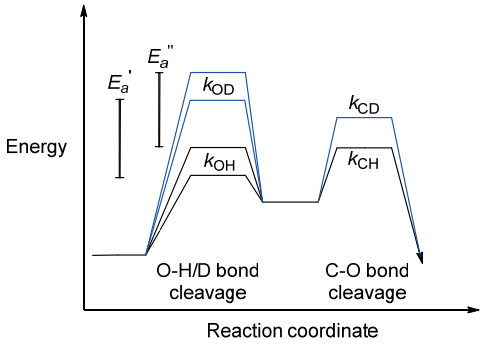
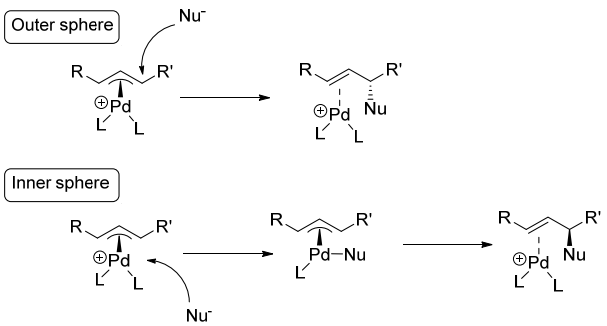


Figure 14. Energy diagram of the O–H bond and the C–O bond cleavages.

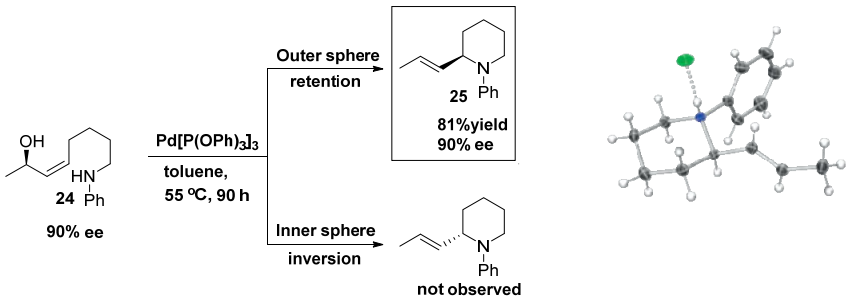
3.2.4 The C–N bond forming step

We were also interested in the C–N bond forming step of the reaction mechanism. A question we would like to answer was whether the nucleophile interacts with the metal prior to the attack. After the π-allylpalladium intermediate is generated, there are two possible mechanisms for the nucleophilic attack by the amine. Either an "outer-sphere" mechanism without prior coordination of the amine to the palladium may occur, or an "inner-sphere" mechanism in which the amine coordinate the palladium prior to the attack of the allyl may occur. A way to distinguish between these two pathways is to use an enantioenriched alcohol and study the stereochemical outcome of the substituted product. In an outer-sphere mechanism, a conservation (double inversion) of the stereocenter is expected and in the inner-sphere mechanism the configuration is expected to inverse. In our case, the amination might be reversible, and the amine may attack at two different positions. Therefore, we needed to design a substrate that would overcome both these two problems.



Scheme 17. Inner-sphere and outer-sphere mechanisms.

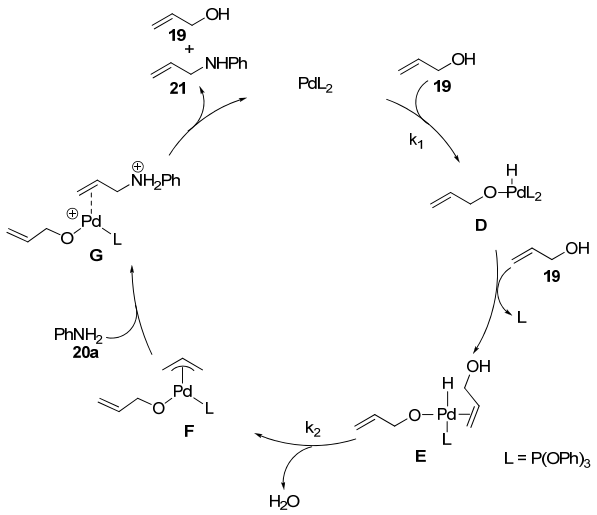
Enantiomerically enriched allylic alcohol (***R,Z***)-**24** was synthesized. For this substrate, the attack by an intramolecular aniline derivative is both favored at one of the two possible positions of the π-allyl and the attack is expected to be irreversible. Compound (***R,Z***)-**24** was subjected to 2 mol% of $Pd[P(OPh)_3]_3$ in toluene at 55 °C for 90 hours. The allylic substitution of (***R,Z***)-**24** proceeded with an overall retention of stereochemistry (double inversion), as determined by chiral HPLC and single-crystal X-ray analysis of hydrochloride salt of piperidine ***(R,E)*-25**. The formation of (***R,E***)-**25** indicated that the reaction proceeded *via* an outer-sphere mechanism. Furthermore, the palladium-catalyzed intramolecular amination of (***R,Z***)-**24** to (***R,E***)-**25** proceeded with complete chirality transfer.



Scheme 18. Synthesis of (*R,E*)-1-phenyl-2-(prop-1-enyl) piperidine (***R,E*)-25** and X-ray structure of piperidine **(*R,E*)-25**·HCl**.**

3.2.5 Proposed reaction mechanism

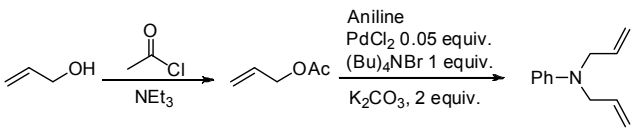
We have proposed a reaction mechanism for the palladium-catalyzed direct amination of allylic alcohols (Scheme 19). Palladium inserts into the O–H bond of **19** to generate palladium hydride intermediate **D**. This step has an activation barrier which is either negligibly lower or equal to the rate-determining step ($k_2 \geq k_1$). This is consistent with the observed primary KIE for the O–H bond cleavage (k_{OH}/k_{OD} = 2.05). The palladium hydride intermediate (**D**) coordinates to a second molecule of **19** to generate intermediate **E**, which is proposed to be responsible for the cleavage of the C–O bond of **19** to generate the π-allylpalladium intermediate **F**.[66] This barrier is visible by a large secondary KIE (k_{CH}/k_{CD} = 1.34) with the deuterated **19-$C_\alpha D_2$** compound, but not with the doubly deuterated **19-$C_\alpha D_2$OD** (k_{CHOH}/k_{CDOD} = 2.06), in accordance with the proposed that the C–O bond cleavage occurs after the O–H bond cleavage. The second-order dependence in **19** is also consistent with two separate steps with equal energy barriers ($k_2 \geq k_1$). Addition of an aromatic amine to either terminal carbon of the π-allyl occurs *via* an outer-sphere mechanism, without prior coordination to palladium to generate intermediate **G**, consistent with the observed double inversion in transforming alcohol (***R,Z*)-24** to (***R,E*)-25**. Proton transfer from the amine and ligand exchange produce the allylamine and regenerate the $Pd[P(OPh)_3]_2$.



Scheme 19. Proposed mechanism for Pd-catalyzed direct aminations of allylic alcohols (**19**).

3.3 Synthetic application in the synthesis of pyrrolines

As seen in the previous paragraph, the $Pd[P(OPh)_3]_3$ based catalytic system has synthetic relevance in the synthesis of enantioenriched piperidines. We wanted to explore other synthetic routes using the $Pd[P(OPh)_3]_3$ complex for non-activated allylic alcohols. Recently, palladium-catalyzed aminations of allylic compounds, such as acetates and carbonates, followed by ring-closing metathesis to generate the corresponding pyrrolines have been reported.[67,68] However, this procedure generated stoichiometric amounts of waste both in the activation step of the alcohol and also in the substitution reaction, where a base was needed (Scheme 20). Therefore, the development of a direct catalytic substitution of alcohols, which produces the desired products, followed by ring-closing metathesis, would generate the corresponding pyrrolines with ethane and water as only by-products.

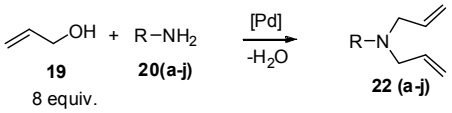


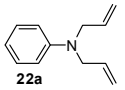
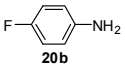
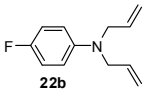
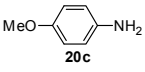
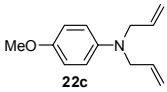
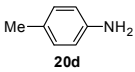
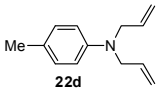
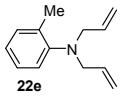
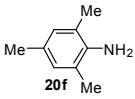
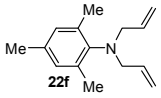
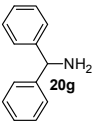
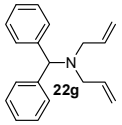
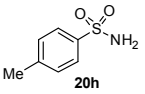
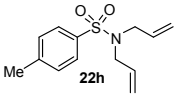
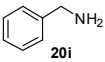
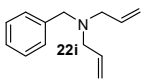
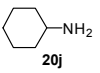
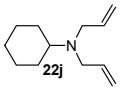
Scheme 20. Literature example of allylation reaction.

3.3.1 Substrate scope for direct catalytic amination of allylic alcohols

The scope of amines was investigated. Most diallylated products were isolated by column chromatography in good to excellent yields (Table 5). Model substrate **20a** was allylated in 1 hour, using 2 mol% of $Pd[P(OPh)_3]_3$ to furnish diallylated aniline **22a** in 95% isolated yield. Steric hindrance of the aniline derivative in *o*-position was observed to affect the chemical yields (Table 5, entries 5 and 6). In the case of the *para*-methoxy sustituted aniline (**20c**), 5 mol% of $Pd[P(OPh)_3]_3$ was used and the diallylated product was generated in full conversion after 4 hours (Table 5, entry 3). Attempts to isolate the product by column chromatography led to decomposition. The diallylation of electron deficient *para*-toluenesulfonamide (**20h**) proceed in 40% yield after 18 hours using 10 mol% of catalyst. The major side product was the monoallylated amide. The lower reactivity may be explained by the lower nucleophilicity of the sulfonamide. The diallylation of benzylamine (**20i**) did not proceed using $Pd[P(OPh)_3]_3$ as catalyst. One explanation is that **20i** or product (**22i**) coordinates palladium and inhibits catalysis. Instead $Pd[P(OPh)_3]_3$ was exchanged for a catalytic system comprising $Pd(OAc)_2$, P^nBu_3, and BEt_3. With this catalyst, both benzyl- and alkylamines were efficiently converted into the corresponding products in good yields.

Table 5. Pd-catalyzed allylation of amines.[a]



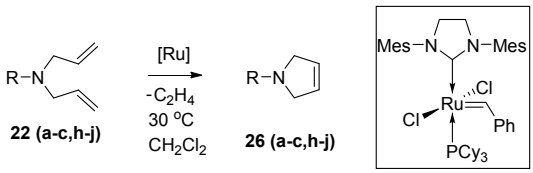
Entry	Substrate	[Pd] (mol%)	Time (h)	Product	Yield(%)
1	 **20a**	2	1	 **22a**	95
2	 **20b**	2	8	 **22b**	98
3	 **20c**	5	4	 **22c**	>95[b]
4	 **20d**	2	4	 **22d**	95
5	 **20e**	2	8	 **22e**	57
6	 **20f**	10	10	 **22f**	52
7	 **20g**	2	22	 **22g**	88
8	 **20h**	10	6	 **22h**	40[b]
9	 **20i**	5	15	 **22i**	97[c]
10	 **20j**	5	19	 **22j**	92[c]

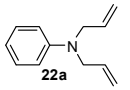
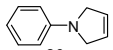
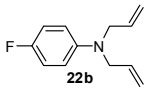
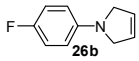
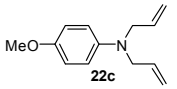
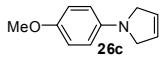
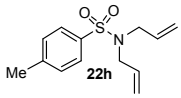
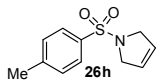
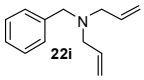
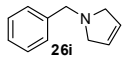
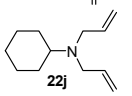
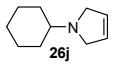
[a] The reactions were performed using 7 mmol of **19**, 0.875 mmol of amine, and 2 mol% of $Pd[P(OPh)_3]_3$ in 1.25 mL of toluene at 80 °C. Yields refer to isolated yields. [b]Conversion by ^1H NMR. [c]The reactions were performed using 7 mmol of **19**, 0.875 mmol of amine, and 5 mol% of $Pd(OAc)_2$, 20 mol% P^nBu_3, and 22 mol% of BEt_3 in 2 mL of THF at 66 °C.

3.3.2 Ring-closing metathesis of diallylated amines

Ring-closing metathesis of the diallylated amines was accomplished with the use of Grubbs catalyst $(H_2IMes)(PCy_3)Cl_2RuCHPh$ (Table 6) to prepare pyrrolines in good to excellent yields. The reactions were monitored by ^1H NMR by integrating known signals of the starting material and the product using mesitylene as internal standard. Substrate **22a** was transformed into N-phenyl pyrroline (**26a**) in above 95% conversion within 1 hour at 30 °C using 2 mol% of catalyst. In the case of the diallylated *para*-methoxy aniline **22c**, a crude mixture from the diallylation was used and RCM provided a mixture desired pyrroline **26c** and pyrrole (**26c′**) in 85% conversion. The more basic benzylamine derivertive **22i** required protonation by HCl prior to RCM. The RCM was performed in a capped tube under microwave irradiation at 50°C for 90 min to generate the pyrroline (**26i**) in 70% conversion. After protonation, the diallylated cyclohexylamine was converted to a 3:2 mixture of pyrrole and pyrroline (**26j**) in 70% conversion.

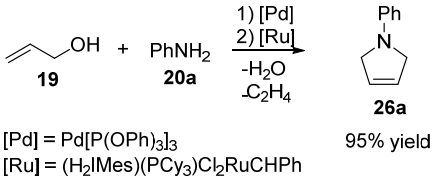
Table 6. Ruthenium-catalyzed ring-closing metathesis.[a]



Entry	Substrate	[Ru] (mol%)	Time (h)	Product	Conv (%)[b]
1	 **22a**	2	1	 **26a**	>95
2	 **22b**	2	12	 **26b**	>95
3	 **22c**	5	12	 **26c**	85
4	 **22h**	2	1	 **26h**	>95
5	 **22i**	10	1.5	 **26i**	70[c]
6	 **22j**	10	1	 **26j**	70[c]

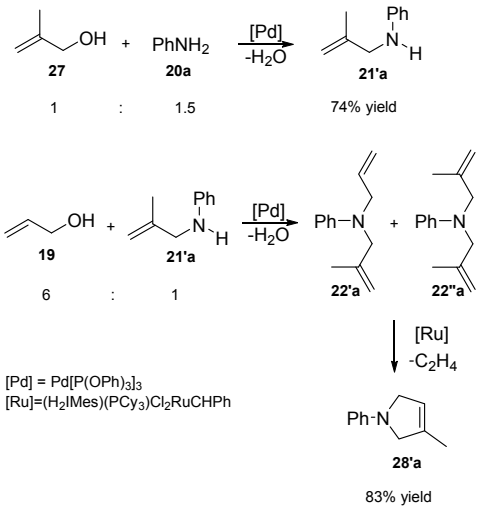
[a]Reactions were performed using 5×10^{-5} mol of diallylated amine and 2-10 mol% of $(H_2IMes)(PCy_3)Cl_2RuCHPh$ in CH_2Cl_2 at 30 °C. [b] The yield was determined by ^1H NMR using mesitylene as internal standard. [c]Reactions were performed using microwave irradiation at 50 °C.

To evaluate the practical utility of the methodology, the allylation reaction of aniline (1 mL) was performed using 2 mol% of $Pd[P(OPh)_3]_3$ at 80 °C for 4 hours (Scheme 21). The unpurified crude mixture of *N,N*-diallylaniline was treated with 5 mol% of $(H_2IMes)(PCy_3)Cl_2RuCHPh$ at 30 °C, yielding 1-phenyl pyrroline **26a** in 95% yield by column chromatography. By this, one purification step was reduced and this improves the environmental factor of the overall reaction.



Scheme 21. A scale-up synthesis of pyrroline.

To expand the substrate scope in respect to the allylic alcohol was desired. This would lead to an unsymmetical pyrroline after ring-closing netathesis. Extension of the methodology to synthesize 3-methyl-1-phenyl pyrroline (**28′a**) was successfully developed in the next step (Scheme 22). Substrate **20a** was monoallylated by 2-methyl-2-propen-1-ol (**27**) using 2 mol% of $Pd[P(OPh)_3]_3$ at 80 °C in 74% isolated yield. The corresponding *N*-(2-methyl-2-propenyl)aniline (**21′a)** was allylated by **19** to afford *N*-(2-methyl-2-propenyl)(allyl)aniline (**22′a)** and *N*-(2-methyl-2-propenyl)$_2$aniline (**22″a**). These two compounds cannot be easily isolated from each other by column chromatography. Instead the mixture was treated with 2 mol% $(H_2IMes)(PCy_3)Cl_2RuCHPh$ where **22′a** was ring-closed at a higher rate to generate the trisubstituted pyrroline in favor of generating the tetrasubstituted pyrroline from *N*-(2-methyl-2-propenyl)$_2$aniline. After purification by column chromatography the desired 3-methyl-1-phenyl pyrroline (**28′a**) was isolated in 83% yield.



Scheme 22. Synthesis of 3-methyl-1-phenyl pyrroline (**28′a**).

3.4 Conclusions

The pure $Pd[P(OPh)_3]_3$ and $Pd(dba)[P(OPh)_3]_2$ complexes have been prepared and isolated. Both complexes have been studied by ^{31}P NMR spectroscopy and X-ray crystallography. The crystal structures revealed that both complexes exhibit a trigonal planar arrangement of the ligands. Equilibrium studies of $Pd(dba)_2$ and $P(OPh)_3$ showed that at room temperature the $Pd[P(OPh)_3]_3$ is more favored than $Pd(dba)[P(OPh)_3]_2$ and $Pd[P(OPh)_3]_4$ complexes. At temperatures below -40 °C the $Pd[P(OPh)_3]_4$ complex becomes visible in the ^{31}P NMR spectrum and at lower temperature the tetracoordinated complex becomes the major species in solution. The catalytic activity of the pure $Pd[P(OPh)_3]_3$ and $Pd(dba)[P(OPh)_3]_2$ complexes has been evaluated in the palladium-catalyzed aniline allylation by allylic alcohol. Comparing the pure complexes $Pd[P(OPh)_3]_3$ and $Pd(dba)[P(OPh)_3]_2$ as catalyst precursors in catalysis showed that the $Pd(dba)[P(OPh)_3]_2$ complex is in fast equilibrium with the $Pd[P(OPh)_3]_3$ that is the most reactive precursor to generate the reactive $Pd[P(OPh)_3]_2$ complex.

The mechanism of palladium-catalyzed direct amination of allylic alcohol has been explored. Labelling experiments support a reaction mechanism involving a π-allylpalladium intermediate instead of a hydrogen autotransfer pathway.

Kinetic studies indicate a first-order dependence on the concentration of palladium complex, a second-order dependence on the concentration of allylic alcohol, and independence on the concentration of aniline and water. These experiments rule out that ammonium or water facilitate the C–O bond cleavage. The kinetic isotope effect studies gave a primary kinetic isotope effect for allylic alcohol with deuterium in the protic position and a relatively high secondary kinetic isotope effect for allylic alcohol with deuterium in the alpha position. Noteworthy, the combined kinetic isotope effect for allylic alcohol with deuterium in both protic and alpha positions was similar to the primary kinetic isotope effect determined. These data rule out that the role of the second allylic alcohol is to facilitate the C–O bond cleavage. A chiral transfer experiment supports an outer-sphere mechanism for the nucleophilic attack by the amine without prior coordination to palladium.

A reaction mechanism is proposed where the palladium inserts into the O–H bond of allylic alcohol, giving rise to a primary kinetic isotope effect. Another molecule of allylic alcohol coordinates to the palladium hydride species. We propose that the palladium hydride species is responsible for the C–O bond cleavage of the second molecule of allylic alcohol, with an activation energy barrier similar to the O–H bond cleavage. This is in agreement with the second order rate-dependence in allylic alcohol. The terminal carbons of the generated π-allylpalladium intermediate is then attacked by the amine without prior coordination to the metal.

We have developed a method to access pyrrolines *via* palladium-catalyzed allylic amination followed by a ring-closing metathesis. A one-pot procedure where aniline was converted to *N*-phenyl pyrroline in 95% overall conversion was demonstrated. The only side-products in this reaction is one equivalent of water and ethene. Unsymmetrical 3-methyl-1-phenyl-pyrroline was conveniently synthesized using a similar protocol in overall 61% yield.

4. Concluding Remarks

The methods that are currently available for utilizing alcohols as starting material in organic synthesis are usually unsustainable. Hopefully, it will not take 100 years to be at the same stage of methodology development as we are today with the oil-derived hydrocarbons.

The goal of the research presented in this thesis was to increase the understanding of the elementary steps of the carbon–oxygen bond cleavage in alcohols by transition metal catalysis. We have chosen two different catalytic systems and two types of alcohols, as model systems. One of the catalytic systems is termed transfer hydrogenolysis in which the hydroxyl group of benzylic alcohols is reductively cleaved. In the other catalytic system, the Tsuji-Trost reaction, the hydroxyl group is substituted by an amine.
Interestingly, there are similarities and differences in the carbon–oxygen bond cleaving event in the two catalytic systems. No reaction was found that convert the hydroxyl group into a better leaving group or any other activation of the hydroxyl group prior to the carbon–oxygen bond cleavage, in any of the catalytic systems.

Furthermore, both catalytic systems make use of a palladium-hydride species to facilitate the carbon–oxygen bond cleavage. In one of the systems, the hydride is derived from the nucleophile and in the other system the hydrogen originates from a proton of the hydroxyl group.

Differences between the two catalytic systems include the rate-determining step. In the heterogenously catalyzed transfer hydrogenolysis of benzylic alcohols by formic acid, the rate-determining step was the transfer of a hydride from the hydrogen donor to the surface of the catalyst. In this catalytic system, the carbon–oxygen bond cleavage is not involved in the rate-determining step.

In the Tsuji-Trost reaction of allylic alcohols, there are two steps that have similar activation energy barriers. The first barrier is the cleavage of the hydrogen–oxygen bond in the hydroxyl group. This can be considered similar to transfer hydrogenolysis. The second barrier is the carbon–oxygen bond cleavage that shows up in the rate-equation as well as the deuterium kinetic isotope effect.

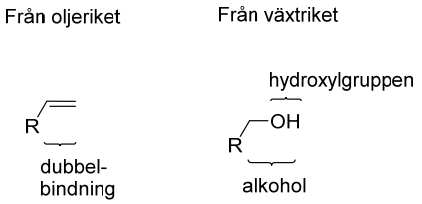
Another difference between the two catalytic systems is the interaction of the nucleophile with the catalyst. As mentioned above, a hydride is transferred to the surface of palladium, in the transfer hydrogenolysis reaction,

and the nucleophile interacts with the catalyst prior to the reaction with the alcohol.

In the Tsuji-Trost reaction, the nucleophile does not interact with the palladium prior to the attack on the π-allylpalladium intermediate. Instead an outer-sphere mechanism is proposed based on the chirality transfer experiments.

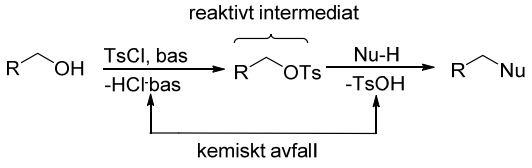
Summary in Swedish

Idag kan kemister syntetisera väldigt komplexa molekyler med hjälp av tekniker som främst har utvecklats under 1900-talet. Dessa tekniker har utvecklats specifikt för oljebaserade kolkällor som huvudsakligen innehåller dubbelbindningen som funktionell grupp efter raffinering (Figur 1). Ett alternativ till de ändliga oljebaserade kolkällorna är de förnybara kolkällorna från växtriket. För att kunna använda dessa, så måste de kemiska metoderna ändras i grunden eftersom växtriket huvudsakligen är uppbyggt av alkoholer till skillnad från oljan som är uppbyggd av kolväten (Figur 1).



Figur 1. Oljerikets kolkällor innehåller dubbelbindningar och växtrikets kolkällor innehåller ofta alkoholer

Alkoholer har en kol-syre (C–O) bindning mellan kolet och hydroxyl (OH) gruppen som är relativt svår att klyva. De tekniker som finns idag konverterar OH-gruppen i ett extrasteg till en ester eller en halid vilka är lättare att klyva (Schema 1). Dessa intermediat är väldigt reaktiva och ofta cancerogena. Dessutom leder dessa reaktioner till att det dagligen genereras tonvis med kemiskt avfall i industrier runt om i världen när C–O bindningen ska klyvas med rådande teknologier. För att kunna nyttja växtriket som kolkälla så måste nya och hållbara tekniker utvecklas.

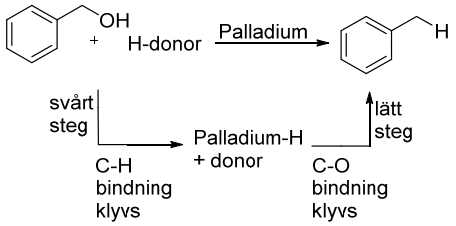


Schema 1. Växtrikets kolkällor innehåller ofta alkoholer

Att utveckla hållbara tekniker för klyvning av C–O bindningar i alkoholer är inget man gör i en handvändning. Istället behövs grundliga studier för att förstå hur C–O bindningen i alkoholer kan klyvas på ett effektivt sätt. Grunden till att utveckla hållbara metoder är att använda katalysatorer som sänker aktiveringsenergin för processen och som inte förgås under den kemiska reaktionen. En katalysator kan hjälpa till att aktivera OH-gruppen eller till och med klyva C–O bindningen.

Huvudmålet för arbetet i denna avhandling är att öka förståelsen för hur en metallkatalysator klyver C–O bindningen i alkoholer där två olika modellsystem har använts. I det första systemet har en heterogen palladiumbaserad katalysator (Pd/C) använts för att klyva C–O bindningen i bensyliska alkoholer. I det andra systemet har en homogen palladiumbaserad katalysator använts för att klyva C–O bindningen i allyliska alkoholer.

I den första delen av avhandlingen har jag studerat hur C–O bindningen klyvs i ett system där bensyliska alkoholer har reducerats till kolväten som har applikationer i att konvertera biomassa till biodrivmedel. Intressant, så visade det sig att vår initiala hypotes att klyvningen av C–O bindningen skulle vara det mest energikrävande steget var fel. Istället var det ett försteg där en kol–väte (C–H) bindning i reduktionsmedlet klyvs som var det hastighetsbestämmande steget för hela processen (Schema 2). Vi hittade även att ett additiv behövdes för processen. Det visade sig att utan additivet så skedde en annan reaktion som var mycket snabbare än den önskvärda. Vi föreslår att additivets roll är att modifiera katalysatorn så att inte fel substrat ska nå katalysatorn först.



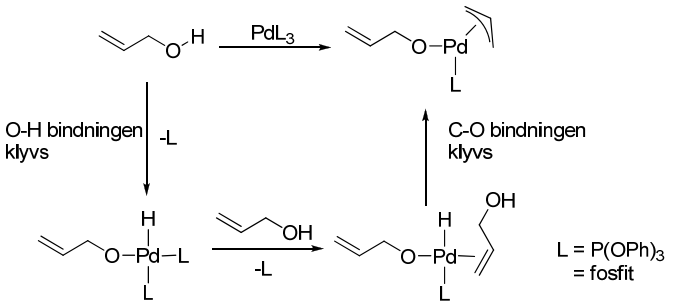
Schema 2. Föreslagen reaktionsmekanism för reduktion av bensyliska alkoholer

I det andra katalytiska systemet har jag studerat hur C–O bindningen klyvs i allyliska alkoholer med en annan katalysator och där OH-gruppen substitueras med en amin. Denna reaktion har applikationer i finkemikalie- och läkemedelsindustrin där aminer är vanligt förekommande.

Katalysatorn som har använts är uppbyggd av palladium med elektronfattiga arylfosfitligander. Ligander används för att skräddarsy en katalysator för en given process, och i vårt system är det att klyva C–O bindningen i allyliska alkoholer. Dessa katalysatorer är inte så vanliga så vi har studerat dem lite extra. De elektronfattiga arylfosfitliganderna ger katalysatorn en unik karak-

tär. Vi hittade ett beroende där antalet ligander bundna till metallen beror på temperaturen där bara tre ligander är bundna till metallen vid rumstemperatur. Vanligtvis är denna siffra fyra.

Vi studerade i detalj hur denna katalysator aktiverade den allyliska alkoholen och har föreslagit en unik reaktionsmekanism där den allyliska alkoholen har två roller (Schema 3). Det finns två steg i denna reaktion som har ungefär lika stora energibarriärer. Det första hastighetsbestämmande steget är när katalysatorn klyver syre–vätebindningen i OH-gruppen i en allylisk alkohol. Det andra hastighetsbestämmande steget är när katalysatorn klyver C–O bindningen mellan kolet och OH-gruppen på den andra allyliska alkoholen



Schema 3. Föreslagen reaktionsmekanism för klyvning av C–O bindningen i allyliska alkoholer

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