Ligand Dependent Regioselectivity in Palladium Mediated Allylic Alkylation

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To my family

Abstract

In this thesis, different aspects on ligand dependent regioselectivity in palladium mediated allylic alkylation have been studied.

It is believed that the regioselectivity is a result of nucleophilic attack trans to phosphorous when applying ligands wih different donor atoms. The regioselective memory effect (regioretention) was studied in cationic systems utilizing a non-chiral P,N-ligand. The experimental findings showed only a small memory effect arising from the preferred attack of the nucleophile on the allylic moiety trans to phosphorous in the ligand. The reason for the low regioretention in the reaction was shown to be due to an anion assisted apparent rotation of the η^3-allyl intermediate.

To minimize the dynamic processes, such as apparent rotation, pre-formed (η^3-allyl)Pd complexes containing a tethered ligand and an auxiliary ligand were applied in the allylic alkylation using malonate nucleophiles. The regioselectivity was shown to depend mainly on steric interactions rather than the electronic effects from the different ligands. In the complexes with less steric interactions, selectivity arising from the trans effect from the ligands could be achieved.

The structure of the tethered (η^3-allyl)Pd complexes in solution were determined by ^{1}H-NMR spectroscopy, and the solid state structures were studied by X-ray diffraction spectroscopy. It has previously been reported that the longest Pd-C bond in the allylic moiety is the more reactive. Therefore, the Pd-C bond lengths in the complexes were compared with the reactivity of the different allylic positions in the alkylation reaction using sodium dimethyl malonate as nucleophile. However, no direct correlation was observed between the reactivity and the Pd-C bond lengths in the allylic moiety.

A tethered (η^3-allyl)Pd complex was used as a probe for the comparison of trans effects arising from different substituted pyridine derivates. Preliminary results showed a decrease in trans effect from the pyridine ligands bearing electron donating substituents.

Keywords: Palladium, allylic alkylation, (η^3-allyl)palladium complexes, regioselectivity, PN-ligand, memory effects, dynamics, ligand effects, trans effects.

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List of publications:

This thesis is based on the following papers, which are referred to by their Roman numerals. Reprints were made with permission from the publishers.

I. **Memory and dynamics in Pd-catalyzed allylic alkylation with P,N-ligands**
Charlotte Johansson, Guy C. Lloyd-Jones, Per-Ola Norrby
Tetrahedron: Asymmetry, **2010**, *21*, 1585-1592.

II. **Sterically governed selectivity in palladium-assisted allylic alkylation**
Jonatan Kleimark, Charlotte Johansson, Sverker Hansson, Björn Åkermark, Per-Ola Norrby.
Submitted to Organometallics

III. **Interplay between strain and steric interactions in palladium-assisted allylic alkylation**
Charlotte Johansson, Per-Ola Norrby
Manuscript

IV. **Structure-reactivity relationship in palladium-assisted allylic alkylation with a tethered ligand**
Charlotte Johansson, Susanne Olsson, Per-Ola Norrby
Manuscript

V. **The Tsuji-Trost reaction as a probe for quantitative correlations of trans effects from pyridines with Hammett sigma-scales**
Charlotte Johansson, Per-Ola Norrby
Preliminary manuscript

Contribution to the papers:

I. Planned and performed all experiments and analyses. Contributed to the interpretation of the results. Contributed to the writing of the paper.

II. Performed all experiments and analyses. Contributed to the interpretation of the results. Contributed to the writing of the paper.

III. Outlined the study. Planned and performed all experiments and analyses. Wrote the major part of the paper.

IV. Performed all synthesis and crystallization. Contributed to the interpretation of the results. Contributed to the writing of the paper.

V. Outlined the study. Planned and performed all experiments and analyses. Wrote the major part of the paper.

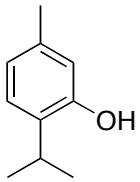
List of abbreviations:

1D	One dimensional
2D	Two dimensional
BINAP	2,2'-Bis(diphenylphosphino)-1,1'-dinaphthyl
BPPFA	1-[2,1'-bis(diphenylphosphino)ferrocenyl] ethylamine
BuLi	*n*-Butyl lithium
COSY	Correlation Spectroscopy
dba	Dibenzylidene acetone
DFT	Density Functional Theory
dppe	Bis(diphenylphosphino)ethane
Et_2O	Diethyl ether
GC/MS	Gas chromatography/Mass spectroscopy
IR	Infrared
L	Ligand
LG	Leaving group
NMR	Nuclear Magnetic Resonance
NOE	Nuclear Overhauser Enhancement
Nu	Nucleophile
OAc	Acetate
PHOX	Phosphinooxazoline
THF	Tetrahydrofuran
TML	Trost Modular Ligand
TMS	Tetramethylsilane

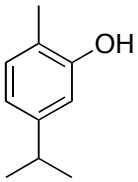
Table of contents

1. Introduction

The ability of controlling the selectivity is an important aspect in organic synthesis. Substances that only differ in the position of a substituent are known as regioisomers. Although the regioisomers look very alike, they might possess different properties. The structures shown in Figure 1 are examples that show how a change in the position of the OH-group can affect the properties of a substance.



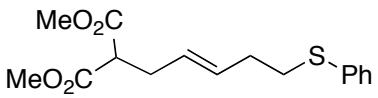
Thymol
mp: 50 °C
Smells like thyme



Carvacrol
mp: 1 °C
Smells like oregano

Figure 1 The regioisomers thymol and carvacrol.

There are several advantages with making reactions selective, most importantly to avoid the separation of unwanted isomers. For example, the regioisomers shown in Figure 2 that are difficult to separate it is most desirable to be able to synthesize each isomer selectively. How to affect the regioisomeric outcome in the palladium mediated synthesis of those two isomers will be discussed later in this thesis.



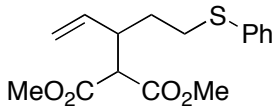


Figure 2 Two regioisomers that are difficult to separate.

1.1 Palladium

1.1.1 The curriculum vitae of palladium

Palladium is a silvery-white metal that belongs to the noble and precious metals. It is positioned among the transition metals, as number 46 in the periodic table and has an atomic mass of 106.4 g/mol. The element palladium was first isolated in 1803 together with rhodium, osmium and iridium from crude platinum by Wollaston and Tennant, who were interested in the refining of platinum.[1] By dissolving crude platinum in *aqua regia*, a small amount of black residue remained and from that residue osmium and iridium were isolated by Tennant. From the solution, Wollaston isolated platinum and thereafter he extracted rhodium and palladium. The latter of the elements was at first named cerecium, after the asteroid Ceres, but was renamed to palladium in honor of the newly discovered asteroid Pallas[†].

Palladium is used in dental alloys, electrical components, and as an alloy with gold in jewelry, known as "white gold", in which only a small amount of palladium is required to decolorize the gold. Palladium is mainly known for its catalytic behavior and almost 60% of the palladium demand is addressed to catalytic processes. Its capability of containing up to 900 times its own volume of hydrogen makes palladium very useful in hydrogen transfer reactions.[2]

1.1.2 Bonding properties of palladium

Palladium belongs to the transition metals and many of these are used in *organometallic* compounds. Such organometallic compounds contain at least one metal-carbon bond, which has a covalent character. A feature of the transition metals is the ability to exist in several oxidation states. For palladium the most common oxidation states are Pd^{0}, Pd^{II}, and Pd^{IV}, but Pd^{I} and Pd^{VI} are also observed.[3] In catalytic cycles of reactions using palladium compounds as catalysts, the oxidation state on palladium usually varies between Pd^{0} and Pd^{II}. Another characteristic feature of transition metals is the presence of *d*-orbitals. The structures of organometallic complexes containing transition metals are directly related to the *d*-orbitals in the valence shell. Palladium has a valence electron configuration of $[Xe]4d^{10}5s^{0}$. When in the oxidation state of Pd^{II}, palladium has lost two electrons, which means that it has one empty *d*-orbital. It is the shape of this *d*-orbital that determines the square planar geometry in Pd^{II} complexes (Figure 3a).[4] On the other hand, in Pd^{0} complexes, where the *s*-orbital

[†] The asteroid itself was named after the Greek goddess Pallas Athena.

is the bonding orbital, the geometry is determined by steric interaction between the ligands.[5] Examples of sterically induced geometries are the tetrahedral geometry of $Pd(PPh_3)_4$ and the linear geometry of $Pd(P\,^tBu_3)_2$ (Figure 3b).

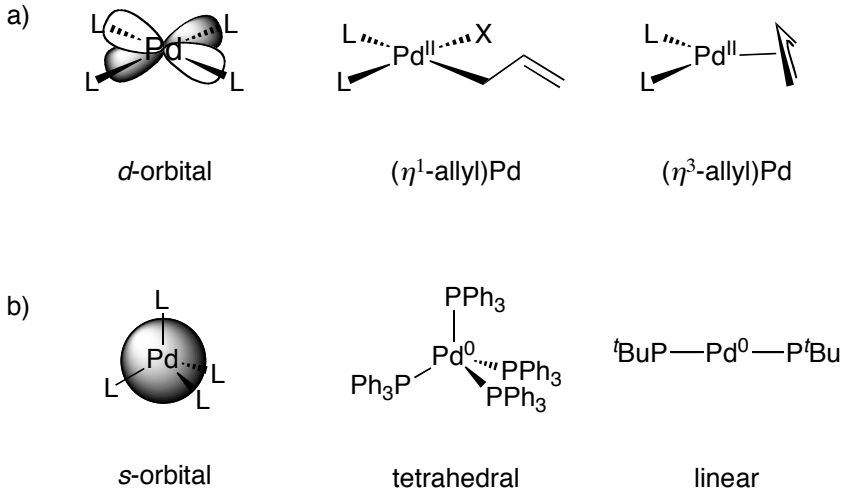
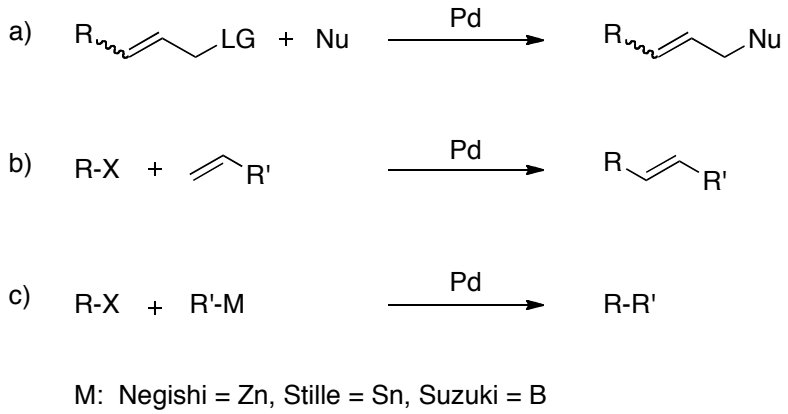


Figure 3 Geometries in Pd complexes; a) Square planar geometry in Pd^{II} complexes b) Geometry determined by steric interaction in Pd^0 complexes.

1.1.3 Palladium in organic synthesis

The first time palladium was used in a commercial homogeneous catalytic process was in the 1950's. The reaction, known as the Wacker process, produces acetaldehyde from ethylene and water, using $PdCl_2$ as catalyst.[6,7] With this process palladium took an important step towards being a versatile catalyst in organic chemistry. Since then palladium has become one of the most frequently used metals in catalysis, especially in C-C bond forming reactions[8], such as the Heck, Negishi, Stille, Suzuki, and the Tsuji-Trost (allylic alkylation) reaction (Scheme 1).[9] An advantage with palladium catalyzed (or mediated) reactions is that they often proceed with high chemo-, regio-, and diastereoselectivity.[9] Most commonly, these reactions occur at sp^2-hybridized carbon atoms on the electrophiles. However, in the allylic alkylation reaction, which is the reaction studied in this thesis, the substitution occurs on an sp^3-hybridized carbon atom via an (η^3-allyl)Pd complex. Another difference from the allylic alkylation concerns the nucleophile, which often is an organometallic compound (Negishi = Zn, Stille = Sn, Suzuki = B) that participates in the reaction via a transmetallation to palladium and the product is formed after a reductive elimination. In the allylic alkylation reaction, the nucleophile is not necessarily an organometallic compound (*vide infra*).

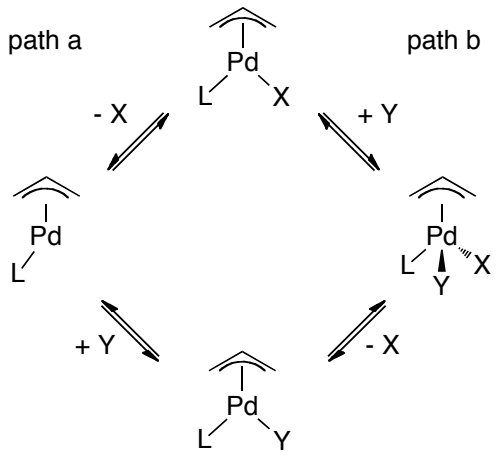


Scheme 1 Schematic representations of a few palladium catalyzed reactions; a) Allylic alkylation, b) Heck reaction, c) Negishi, Stille and Suzuki reactions.

1.2 Dynamic processes in (η^3-allyl)Pd complexes

The (η^3-allyl)Pd intermediates are often relatively stable, and can be isolated and analyzed both in solution and in solid state. In solution, several dynamic processes occur that can be observed using NMR spectroscopy.[10] These can be either an advantage or a problem in the allylation reaction. The processes discussed in this thesis are the following:

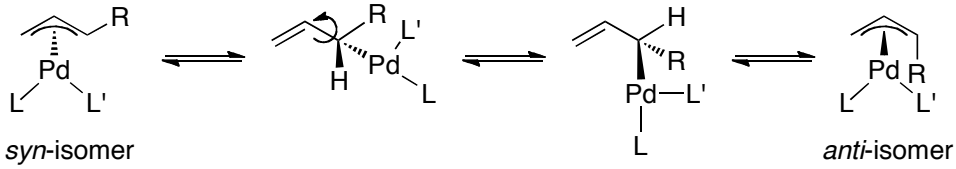
- *Ligand exchange.* In solution, it is possible to exchange one or both of the ligands L and X in the (η^3-allyl)PdLX complex. This exchange can proceed either via a *dissociative* or an *associative* mechanism, Scheme 2.



Scheme 2 Ligand exchange via the dissociative (path a) and the associative (path b) mechanism.

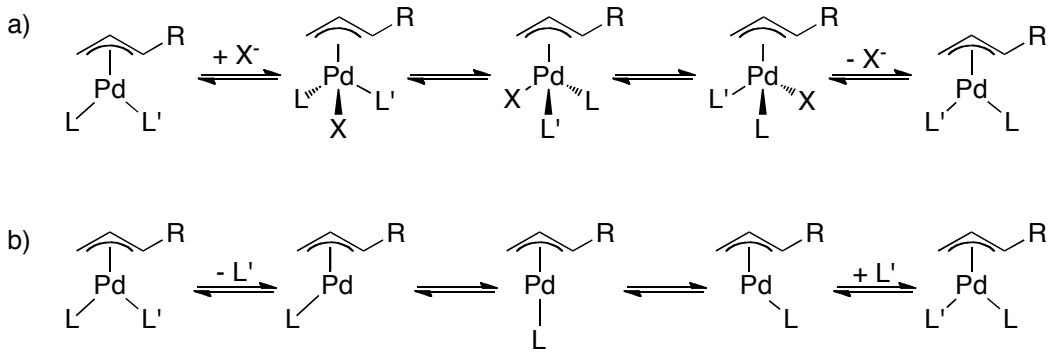
- *Dimerization*. If one of the ligands (X) in the (η^3-allyl)PdLX dissociates, the resulting (η^3-allyl)PdL complex can dimerize into [(η^3-allyl)PdL]$_2$. This is often observed when L = halogen, OAc, $OCOCF_3$ and similar.

- *η^3-η^1-η^3 isomerization (syn-anti isomerization)*. The palladium can coordinate to the allyl in two different modes, either to all three allylic carbons (η^3-allyl)Pd, or to one allylic carbon (η^1-allyl)Pd, (*vide supra*). These two isomeric forms are involved in the η^3-η^1-η^3 isomerization of the allyl. The isomerization occurs via a change in coordination of palladium to the allyl from η^3 to η^1. The C-C bond in the η^1-complex can rotate freely and thereafter the (η^3-allyl)Pd complex can reform, either back to the starting complex or to the complex where one of the termina of the allylic moiety has undergone *syn-anti* isomerization and the other two carbon atoms in the allylic moiety have been inverted (Scheme 3). The rate of η^3-η^1-η^3 isomerization is enhanced by the presence of additional ligands, such as phosphines or halide ions, probably by coordination to Pd and thus stabilizing the η^1-form.[11,12]



Scheme 3 η^3-η^1-η^3 isomerization

- *Apparent rotation (syn-syn, anti-anti isomerization)*. A direct rotation of the Pd-allyl bonds in the (η^3-allyl)Pd complex is not likely in square planar complexes where palladium is coordinated to all three carbons atoms in the allyl moiety. Two different mechanisms have been suggested, an associative pseudorotation[13] as shown in Scheme 4a and a dissociative mechanism[14,15] as shown in Scheme 4b.



Scheme 4 a) Apparent rotation via pseudorotation, b) Apparent rotation via a dissociative mechanism, through a T-shaped intermediate.

1.3 The trans influence and the trans effect

In square planar and octahedral metal complexes, the ligands coordinated to the metal have an effect on the stability of the entire complex. In the complex, every ligand affects the remaining groups coordinated to the metal by electronic influences via the metal. The effect is largest for ligands that are in trans position. This can be explained in terms of orbital overlap, where the ligands in trans positions are coordinating to the metal via one common metal orbital (Figure 4). The stronger one of the ligands binds to the metal, the weaker the bond to the other ligand becomes.[16,17] The influence from the ligand arises from the bonding via a free electron pair on the ligand to the metal (σ-donation), and the back donation from the metal to the ligand (π-accepting).[3] The relative contribution from the σ-donation and π-accepting is dependent on both the ligand and the metal.

Figure 4 The orbital overlap of two ligands coordinated to one metal *d*-orbital.

The weakening of the metal-ligand bond for ligands in the trans position was first described by Chernyaev already in 1926.[18,19] Usually, the thermodynamic and the kinetic influence from the ligand are treated separately:

- The thermodynamic effect, known as the *trans influence*, affects the ground state of the groups in trans position.[3] The ground state properties include

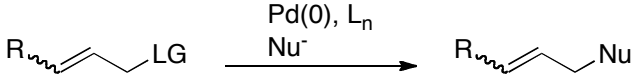
the ligand-metal bond lengths, coupling constants, and vibrational frequencies. The trans influence can usually be measured by standard spectroscopic techniques such as NMR- and IR spectroscopy, and X-ray crystallography.[20]

- The kinetic effect, known as the *trans effect*, affects the transition state, *i.e.* it lowers the reaction barrier. The trans effect is the effect that a certain ligand has on the rate of substitution of the coordinated group trans to the ligand.[3] At first, the effect was only referring to the dissociation of ligands but later it was broadened to include also association of a ligand to the complex. Today, the effect is not only restricted to ligand exchange in metal complexes, but also includes the rate of nucleophilic attack on the coordinating group, for example in allylic alkylation, which will be discussed later in this thesis. To be able to detect the trans effect, the *rate* of the reaction has to be measured. This can sometimes be a challenging task if the reactions are fast. A way of getting around that problem is to perform competitive reactions. By measuring the product distribution, the relative rates can be compared and thus also the trans effect.

When observing similar complexes, the elongated bonds, resulting from the trans influence, are usually the more labile bonds, a result of the trans effect. Thus, the two effects are correlated, but there are examples where the elongated bond is not the more reactive.[21]

1.4 The Tsuji-Trost reaction

The palladium catalyzed allylation reaction (Scheme 5) is frequently used in organic synthesis.[22,23] The Tsuji-Trost reaction is referred to as the alkylation of allylic substrates by stabilized carbanions, such as malonates. The reaction was first reported by Tsuji *et al.* in 1965 using pre-formed (η^3-allyl)Pd complexes.[24] Thereafter, the reaction was further developed by Trost *et al.* by starting from alkenes and using additional phosphine ligands,[25] and later the asymmetric version of the reaction[26] was reported. Further on the reaction was improved by employing the use of allylic acetates and performing the reaction catalytically.[27,28]



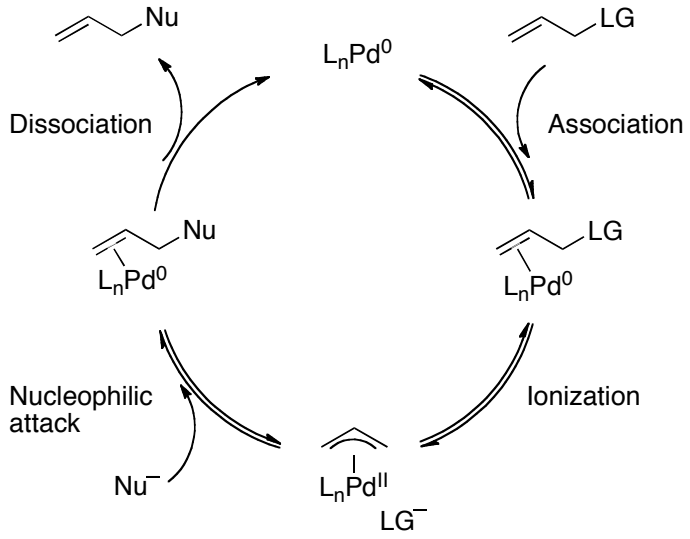
Scheme 5 Palladium catalyzed allylation

The allylic alkylation can be performed under mild conditions at ambient temperature. The most commonly used substrates are allylic acetates, but a variety of leaving groups can be utilized, for example benzoates, carbonates, carbamates, halides, or epoxides.[29,9] A variety of nucleophiles can be applied in the reaction, such as alkali metal enolates or heteroatom nucleophiles, but the most commonly used are soft stabilized carbon nucleophiles, *e.g.* malonates.[29,9]

The allylic alkylation reaction has been the object of numerous investigations, from the scope to the mechanism of the catalytic cycle.[30,31,32] Although several studies have been performed in the area of palladium mediated allylic alkylation, there are still uncertainties needed to be clarified and some of these will be discussed in this thesis.

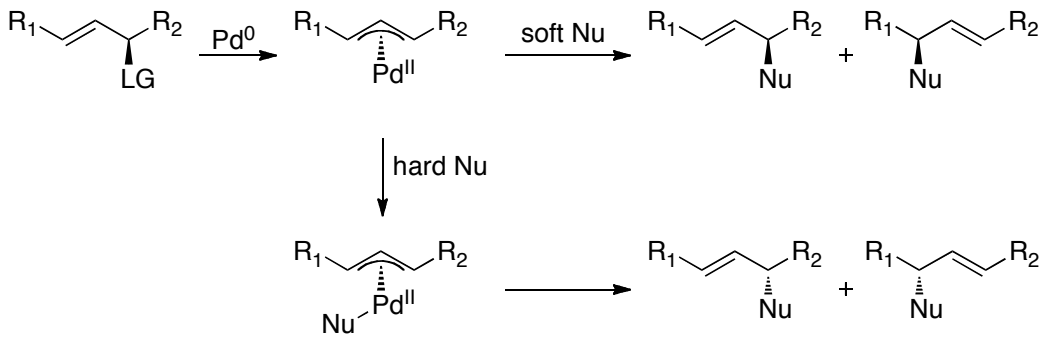
1.4.1 Mechanism and catalytic cycle

The mechanism for the catalytic cycle of the allylic alkylation reaction begins by coordination of the palladium(0) complex to the allylic substrate forming a η^2-complex (Scheme 6). Thereafter, via oxidative addition, an (η^3-allyl)Pd complex with the leaving group as counter ion is formed. The oxidative addition in these types of complexes is also referred to as ionization. The resulting (η^3-allyl)Pd complex reacts with the nucleophile, yielding a η^2-complex between Pd^0 and the product. In the final step, the product is released after dissociation from the Pd^0 complex.



Scheme 6 Catalytic cycle for the palladium catalyzed allylic alkylation.

The ionization step occurs with inversion of configuration and the nucleophilic attack also proceeds with inversion when using soft, stabilized carbon nucleophiles (e.g. malonates) forming the final product with an overall retention in the reaction (Scheme 7). Hard unstabilized carbon nucleophiles (*e.g.* organometallic reagents) react with the η^3-allyl complex by another mechanism: First a transmetallation to Pd occurs and then transfer to an allylic carbon atom by reductive elimination, thus forming the final product with an overall inversion (Scheme 7). Heteroatom based nucleophiles such as amines[32] or alcohols[33] are also feasible and they usually react via inversion, as for the stabilized carbon nucleophiles. Carboxylates can react both as soft and hard nucleophiles, depending on the reaction conditions.[34]



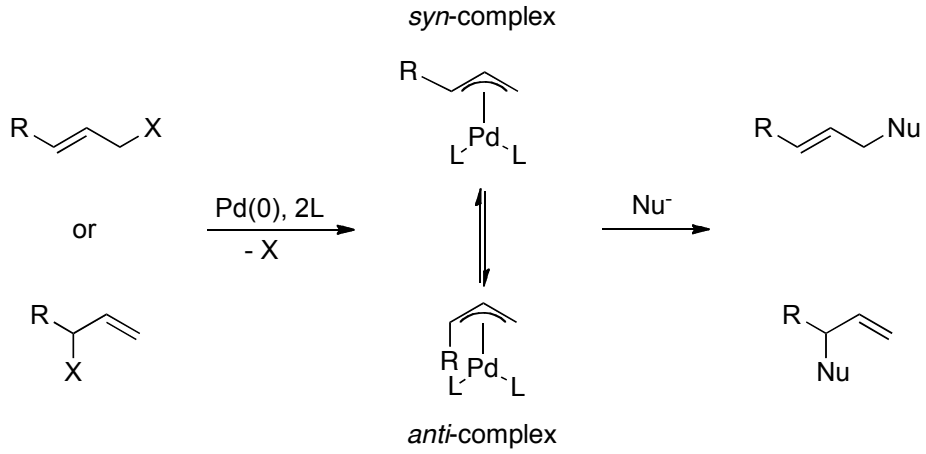
Scheme 7 The stereochemical outcome with soft and hard nucleophiles, respectively.

The oxidative addition step is reversible and the leaving group can re-attack on the η^3-allyl intermediate on either of the allylic carbons, leading to an isomerization of the allylic substrate. [35] This palladium catalyzed stereochemical scrambling of allyls, by reverse oxidative addition, has been the object of several studies.[36,37,38] Another mechanism for stereochemical scrambling of allylic substrates is an S_N2-type attack by Pd^0 on the (η^3-allyl)Pd complex, but this mechanism is slow in catalytic systems, and is inhibited when using bidentate ligands.[39] This inhibition has been observed for example in cyclohexenyl substrates when applying the bidentate ligand dppe.[40] The S_N2-type attack by Pd^0 is also believed to be slowed down by chloride ions.[41] The attack on the allyl by the nucleophile is considered to be an irreversible step when using stabilized carbanions, but exceptions have been observed.[42]

1.4.2 Selectivity

Isomeric starting materials should give rise to the same product distribution, since the reaction proceeds via a common intermediate and the nucleophile can attack either of the two termini of the allyl[30,32] (Scheme 8). The regioisomeric ratio of

the products is influenced by several factors, including the nature of the R-group, the ability of the intermediate to *syn-anti* isomerize, and by the ligands used.[43,44,45]



Scheme 8 Reaction proceeds via an isomerizable, common (η^3-allyl)Pd intermediate.

When applying a monosubstituted allylic substrate, terminal attack of the nucleophile leading to the linear product is the most common result. On the other hand the branched product is sometimes desired due to the possibility of chirality at the substituted carbon atom. Therefore, focus has been put on how to increase the formation of the branched product in the palladium catalyzed reaction. However, by utilizing other metals, such as Ir, Rh, Ru, W and Mo, a difference in selectivity occurs and the branched product is more commonly observed.[9,32]

The allylic carbon atoms in the *syn*- and *anti*-isomers of the (η^3-allyl)Pd have different reactivity. In monosubstituted allylic substrates the resulting *anti*-isomer has a moderate preference for internal nucleophilic substitution whereas the *syn*-isomer has a strong preference for terminal nucleophilic attack.[44] Therefore, by increasing the amount of the desired isomer of the intermediate in the reaction, it is possible to increase the desired selectivity.[43,44,45] The *syn*-isomer is usually more stabile than the *anti*-isomer. However, exceptions are known and the *anti*-isomer has even been isolated by using 2,9-disubstituted phenantroline ligands.[45]

1.4.3 Ligands

The application of ligands in the allylic alkylation reaction has a dual purpose, both activation of the η^3-allyl for nucleophilic attack and control of the selectivity in the reaction. When a ligand with π-accepting ability is applied it can withdraw electrons from the metal, the phenomenon known as back-bonding,[3] and thereby

increasing the positive charge on the η^3-allyl moiety. Thus, the greater the π-accepting ability of the ligand, the more increased is rate of the reaction.[46]

As for many other palladium catalyzed reactions, considerable effort has been made in the area of ligand design to afford the desired regio- and stereoselectivity in the asymmetric allylic alkylation reactions.[22,47,48,49] Many of the bidentate ligands used in the reaction induce selectivity by both steric and electronic effects. Some well known ligands for asymmetric allylic alkylation are the C_2-symmetric BINAP ligand[50] developed by Noyori *et al.* and the modular ligand TML[51] (Trost Modular Ligand), developed by Trost *et al.* (Figure 5). The enantioselectivity is induced by the chiral scaffold of the ligand. Other classes of ligands are non-symmetrical systems containing two different donor ligands. Examples of these are the phosphinooxazoline ligands (*e.g.* PHOX) developed independently by the research groups of Pfaltz[52], Helmchen[53], and Williams[54] (Figure 5). In these ligands the steric bulk directs the position of the substrate with respect to the chiral scaffold and thereafter the donor atom with the largest trans effect is believed to direct the attack of the nucleophile. A third type is the ferrocene based BPPFA ligands, developed by Hayashi *et al.* where the ligand has an additional tether, which directs the attack of the nucleophile.[55]

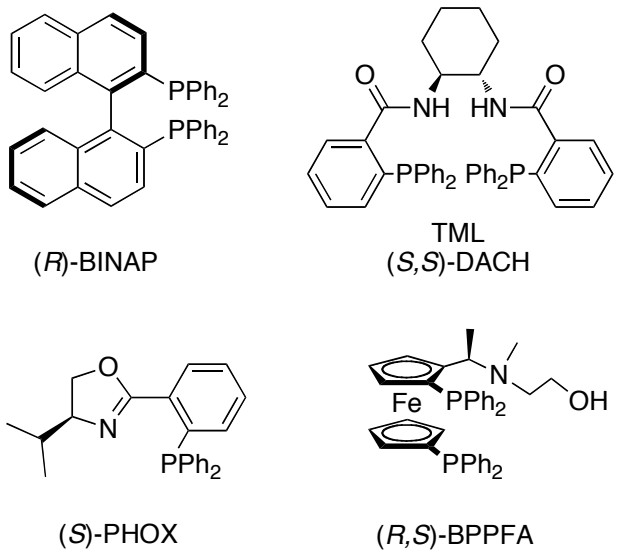
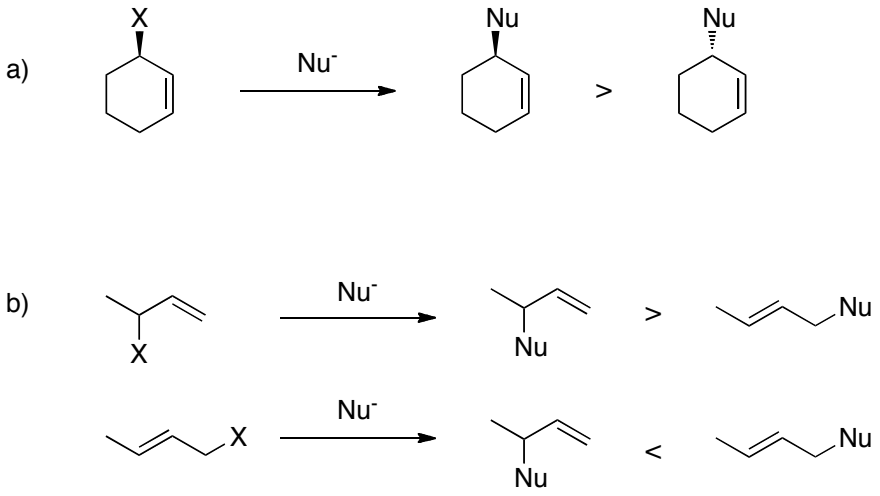


Figure 5. Examples of ligands used for asymmetric allylic alkylation

1.4.4 Memory effects

The alkylation of allylic substrates occurs via (η^3-allyl)Pd intermediates. When all the possible (η^3-allyl)Pd intermediates are in rapid equilibrium and the nucleophilic attack is slow (Curtin-Hammett conditions[56]), regioisomeric substrates give the same product distribution. Therefore, when applying non-chiral ligands and proceeding via a symmetric (η^3-allyl)Pd intermediate, the chiral information is lost. However, in 1981 Fiaud and Malleron observed optically active products when applying chiral cyclohexenyl acetate in the Tsuji-Trost reaction by using non-chiral bidentate phosphorous ligands (dppe and dppb).[57] The phenomenon when chiral information is transferred from the substrate to the product, via the η^3-allyl intermediate, without the use of chiral ligands, is referred to as *stereoselective memory effect* or *stereoretention* (Scheme 9a). This effect has been suggested to originate from tight ion-pairing between Pd and the leaving group, and a directing effect from that leaving group on the nucleophile.[58] Later, it has been shown to originate from differentiations of the electronic properties in the allylic moiety due to different influences from the donor atoms (*e.g.* P, Cl) in the auxiliary ligands.[59,60]

Another type of memory effect is observed when the regiochemical information in the substrate is transferred to the product. This is observed when isomeric starting materials, which should proceed to the product via a common intermediate, give different product ratios.[60] This is referred to as a *regioselective memory effect* or *regioretention* (Scheme 9b).



Scheme 9 a) Stereoselective memory effect, b) Regioselective memory effect.

Although memory effects are considered as a complication in allylic alkylation, as the reaction becomes very sensitive to the choice of allylic substrate, they can

sometimes be considered as a possibility for increased selectivity. In the literature, there are protocols taking advantage of the memory effect, for example in enantioconvergent synthesis,[61] and stereospecific synthesis[62,63] by applying reactive enolate nucleophiles and suppressing the dynamic processes in the (η^3-allyl)Pd intermediate.

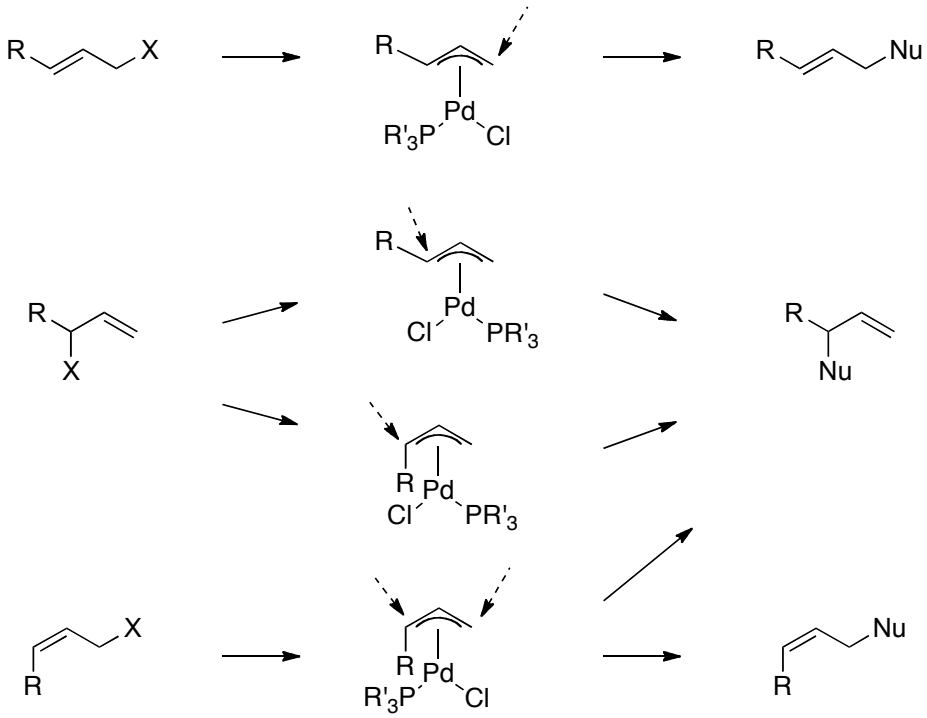
2. Aim of the thesis

The aim of this work has been to investigate factors that affect the regioselectivity in palladium mediated allylic alkylation. The focus has been directed on experimental investigations of the electronic influences from the ligands and how to differentiate them from the steric interactions from the substrates.

3. Regioselective memory effects in palladium catalyzed allylic alkylation (Paper I)

3.1 Introduction and aim

The memory effect has sometimes been considered a complication in allylic alkylations, since it makes the selectivity dependent not only on the ligand but also on the substrate. In a previous study, up to 40% memory effect was observed when using neutral complexes, of the type (η^3-allyl)Pd(PPh_3)Cl.[64] A computational study clearly showed a preference for the nucleophile to attack on the allylic moiety trans to the P-donor atom (Scheme 10). There was only one exception observed, namely the *anti*-isomer, which was more reactive at the internal allylic carbon atom even when positioned trans to Cl.



Scheme 10 Regioselectivity in different (η^3-allyl)PdPPh_3Cl complexes, according to DFT calculations. The arrow marks the site for preferred nucleophilic attack.

Since ligand exchange is commonly occurring in (η^3-allyl)Pd complexes, there will always be an equilibrium between different species when applying more than one coordinating ligand.[10,35] A way to avoid a mixture of complexes with different auxiliary ligands, *e.g.* [(η^3-allyl)Pd(P,P)]$^+$ and [(η^3-allyl)Pd(N,N)]$^+$, is to apply a bidentate ligand. In this study, a non-chiral symmetric bidentate P,N-

ligand (**1**) was used (Figure 6). Furthermore, by utilizing symmetric η^3-allyl systems, originating from **2** and **3**, the selectivity due to steric interactions and the difference in reactivity between the corresponding *syn*- and *anti*-isomers have both been excluded (Figure 6). In addition, by the use of deuterium labeled substrates the regioselectivity in the reaction can be observed by ^{1}H-NMR spectroscopy.

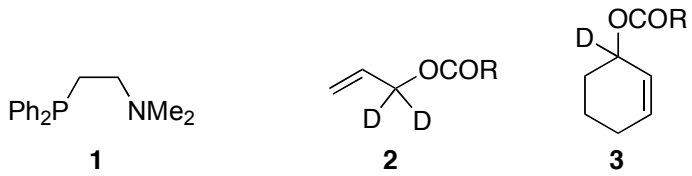
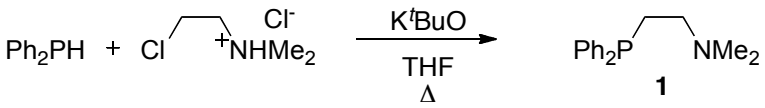


Figure 6 The P,N-ligand **1** and the labeled substrates **2** and **3** utilized in the study.

3.1.1 Synthesis

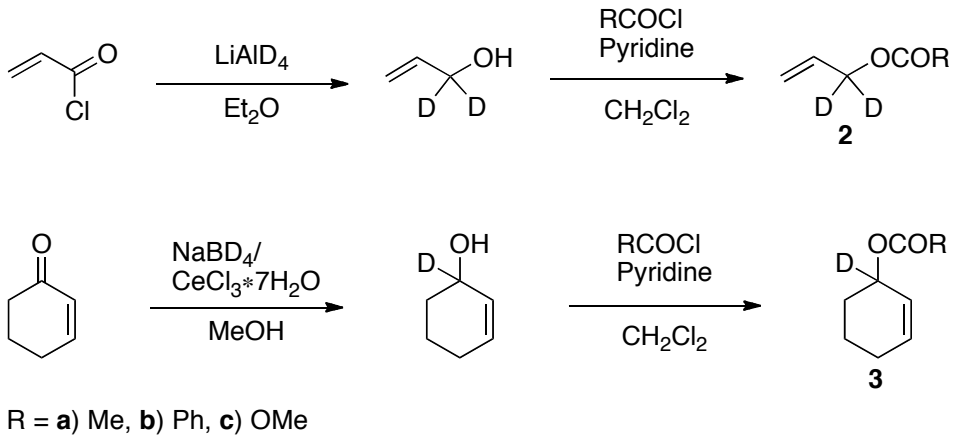
The P,N-ligand **1** was synthesized in 28% yield from 2-chloro-*N,N*-dimethylethylamine hydrochloride and diphenylphosphine, using a modified literature procedure[65] (Scheme 11). The low yield is a result of difficulties in removing oxidized phosphine by-products during the purification.



Scheme 11 Synthesis of P,N-ligand, **1**.

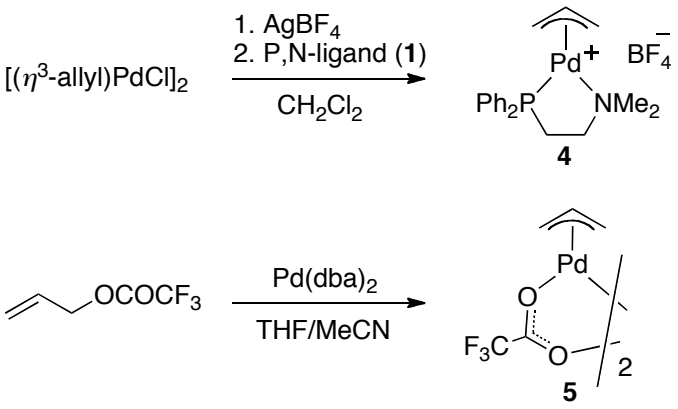
The deuterium labeled allylic substrates were synthesized as depicted in Scheme 12. Attempts to prepare the allyl alcohol by Luche reduction[66] of acryloyl chloride or methyl acrylate gave unsatisfying results. Luche reduction of acrolein gave the desired product, but no product could be isolated due to difficulties during work-up and purification. Finally, the deuterium labeled allylic alcohol was prepared by reduction of acryloyl chloride with $LiAlD_4$ in Et_2O.[67] The crude alcohol was thereafter acylated using pyridine and the appropriate acid chloride in CH_2Cl_2 in an overall yield of 20-35% after distillation using a Hickmann apparatus, or by column chromatography.[64,68] The choice of solvents turned out to be important in both steps of the synthesis. The use of Et_2O instead of THF in the first step is motivated by the low boiling point of allyl alcohol, and using Et_2O thereby enables easier removal of the solvent. In the acylation step, a low boiling solvent was also desired and the highest yields were observed when using CH_2Cl_2. The labeled cyclic substrates (**2a-c**), were prepared by Luche reduction of 2-cyclohexenone to 1-D-cyclohexenol in 90% yield using $NaBD_4$ and $CeCl_3$,

followed by acylation of the resulting alcohol with the appropriate acid chloride in the presence of pyridine in 40-60% yield after column chromatography.



Scheme 12 Synthesis of deuterium labeled allylic substrates, **2a-c** and **3a-c.**

The palladium catalysts used in the allylic alkylation were synthesized as depicted in Scheme 13. [(η^3-Allyl)Pd(P,N-ligand)]BF_4 **4** was prepared from [(η^3-allyl)PdCl]$_2$ and the P,N-ligand **3** in the presence of $AgBF_4$ and collected as bright yellow crystals in 91% yield after removal of the silver salts by filtration and evaporation of the solvent.[45] Attempts to synthesize the complex from [(η^3-allyl)PdOCOCF$_3$]$_2$ and HBF_4*OEt_2 as described by Vitagliano *et al.*,[69] was unsuccessful and led to decomposition of the complex. [(η^3-Allyl)PdOCOCF$_3$]$_2$ (**5)** was prepared from allyltrifluoroacetate and Pd(dba)$_2$ in 90% yield.[69] The [(η^3-allyl)Pd(P,N-ligand)]OCOCF$_3$ complex was formed in situ by adding ligand **1** to a solution of **5**. The isolated complexes, **4** and **5**, are relatively stable and can be handled in air.



Scheme 13 Synthetic routes to the palladium complexes **4** and **5**.

3.2 Results

At first, to confirm the selectivity arising from the trans effect from the phosphorus atom in the ligand, a computational study was performed on the different transition states for the nucleophilic attack on the two termini of the allyl moiety.[†] As expected, the attack trans to phosphorous was favored by approximately 7 kJ/mol. At room temperature this would correspond to a memory effect of over 80%.

The labeled substrates were applied in the reaction, as depicted in Scheme 14. The allylic alkylations were performed at room temperature, under nitrogen atmosphere, for 20 h using sodium diethyl methylmalonate as nucleophile. The product ratios were determined using ^{1}H-NMR spectroscopy by comparing the integrals of the signals from the allylic moiety. When applying the PN-ligand together with $Pd_2(dba)_3$ (catalyst **A,** Figure 7), no regioretention was observed for any of the substrates (entries 1-6 in Table 1).

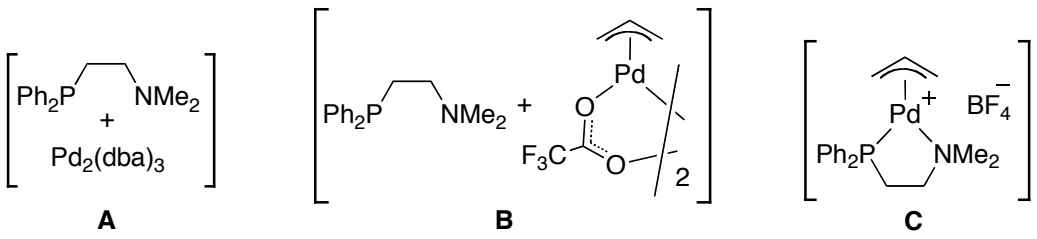
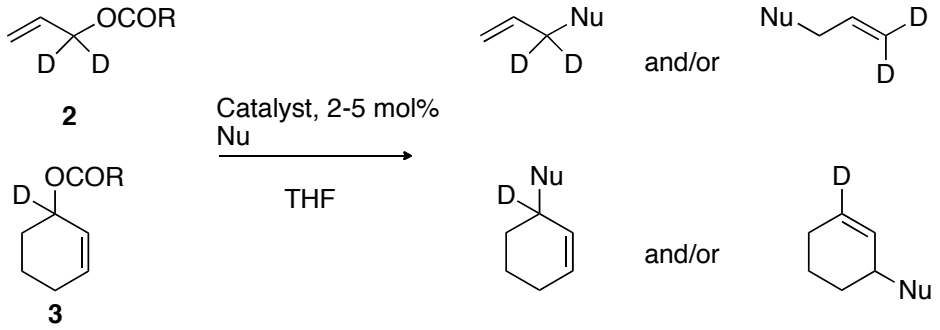


Figure 7 The catalysts utilized in the allylic alkylation.



Scheme 14 The allylic alkylation of **2** and **3** by sodium diethyl methylmalonate using the Pd complexes, depicted in Figure 7.

[†] The DFT computational investigation was performed by Per-Ola Norrby.

Table 1. Results from the allylic alkylation of **2** and **3** by sodium diethyl methylmalonate using catalysts **A-C**.

Entry	Substrate	Catalyst	Retention (%)[#]
1	**2a**	**A**	-2[a]
2	**2b**	**A**	0
3	**2c**	**A**	-2[a]
4	**2a**	**A**	2
5	**3b**	**A**	0
6	**3c**	**A**	3
7	**3a**	**B**	9
8	**3b**	**B**	1
9	**3c**	**B**	7
10	**2a**	**C**	14
11	**2b**	**C**	17
12	**2c**	**C**	8
13	**3a**	**C**	10
14	**3b**	**C**	5
15	**3c**	**C**	6

[a] The memory effect should be a positive number. The small negative numbers arise from minor errors in the integration of the ^{1}H-NMR spectrum.

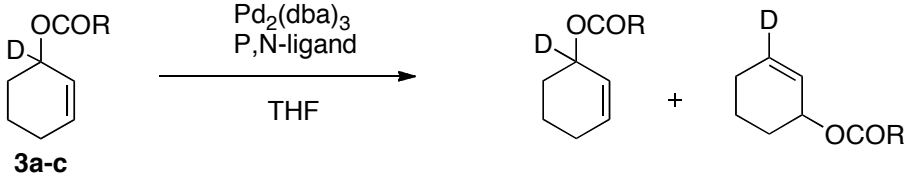
[#] The memory effect is calculated as 100%*(1 - X/Y)/ (1 + X/Y), where X and Y are the two possible isomers.

Amatore and Jutand have shown that when dba is present, an equilibrium between $[Pd^0(dba)(PPh_3)_2]$ and $[Pd^0(PPh_3)_2]$ is established.[70] To negate the possible influence from dba, two alternative catalysts were applied, **B** and **C** in Figure 7. Furthermore, the amount of catalyst was reduced to 2 mol% in order to minimize the amount of diethyl 2-allyl-2-methylmalonate formed by reaction of the nucleophile with the catalyst. The reaction then showed a small regioretention for all the substrates (entries 7-12 in Table 1) which also confirms that dba is not an innocent spectator ligand. Still, the observed regioretention was much lower than the expected result from the computational study. Dynamic processes in the (η^3-allyl)Pd complex, rather than a lack of trans effect from the ligand were more likely to be the explanation for this observation.

3.3 The regioisomeric isomerization of allylic substrates

In one of the experiments, when **3c** was used as substrate, some of the starting material was recovered. Surprisingly, it had isomerized due to a re-attack of the leaving group. In the case where the substrate isomerizes before the nucleophile attacks, no regioretention would be observed. This is not an improbable scenario, since the oxidative addition step has been shown to be reversible and tight ion

pairing has been observed with (η^3-allyl)Pd and acetates in THF.[35] There have also been suggested that the η^2-complex and not the η^3-complex is the resting state in the reaction.[71] To confirm whether all the allylic substrates in the study isomerize under these conditions, a series of experiments with no added nucleophile were performed (Scheme 15).



3a-c

R = Ph or OMe R ≠ Me

Scheme 15 The isomerization of allylic substrates, illustrated with **3**.

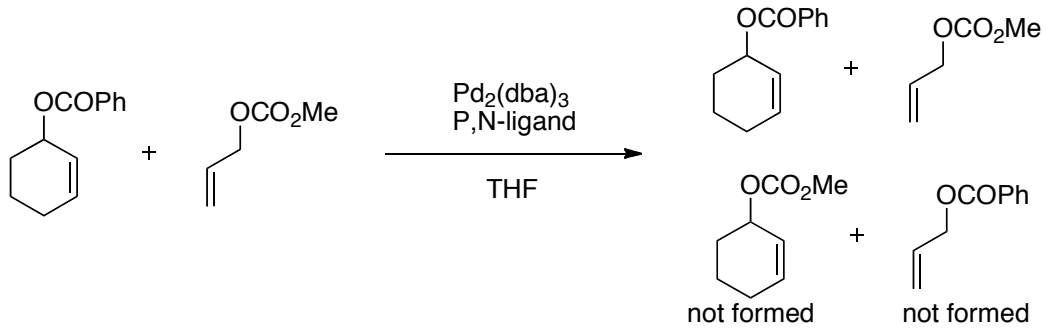
After 65 hours, the reaction mixture was quenched with HCl (1M) and analyzed by ^{1}H-NMR spectroscopy. All substrates (**2a-c, 3b-c**), except the cyclohexenyl acetate (**3a**), gave completely isomerized allyl derivates when using $Pd_2(dba)_3$ as palladium source (entries 1-6 in Table 2). When applying catalysts **B** or **C,** no isomerization of the allyls was observed (entries 7-9 and 13-15 in Table 2). Pd^0 was believed to catalyze the rearrangement of the allylic starting materials. Therefore, another series of experiments were performed, where 0.05 or 0.1 equivalents of nucleophile (sodium diethyl methylmalonate) was added to the reaction mixture in order to produce some Pd^0 in the solution. After 20 h only minor (5-10%) isomerization of all three of the allyls (**3a-c**) was observed when applying catalyst **B** (entries 10-12 in Table 2). However, this was not enough of the isomerized allylic substrate to explain the low regioretention in the allylic alkylation reaction. Still, the small amount of alkylation product formed in the reactions with the added nucleophile showed no regioretention for any of the substrates. These results point to the conclusion that it is not the isomerization of the allylic substrates that is responsible for the low regioretention in the reaction when using **B** as catalyst. When performing the same experiments using catalyst **C**, no isomerization of the allylic substrates was observed (entries 16-18 in Table 2).

Table 2 Results from the isomerization experiments.

Entry	Substrate	Catalyst	Isomerized allyl
1	**2a**	**A**	Yes
2	**2b**	**A**	Yes
3	**2c**	**A**	Yes
4	**3a**	**A**	No
5	**3b**	**A**	Yes
6	**3c**	**A**	Yes
7	**3a**	**B**	No
8	**3b**	**B**	No
9	**3c**	**B**	No
10	**3a**	**B** +0.1 eq. Nu^-	5-10%
11	**3b**	**B** +0.1 eq. Nu^-	5-10%
12	**3c**	**B** +0.1 eq. Nu^-	5-10%
13	**3a**	**C**	No
14	**3b**	**C**	No
15	**3c**	**C**	No
16	**3a**	**C** +0.05 eq. Nu^-	No
17	**3b**	**C** +0.05 eq. Nu^-	No
18	**3c**	**C** +0.05 eq. Nu^-	No

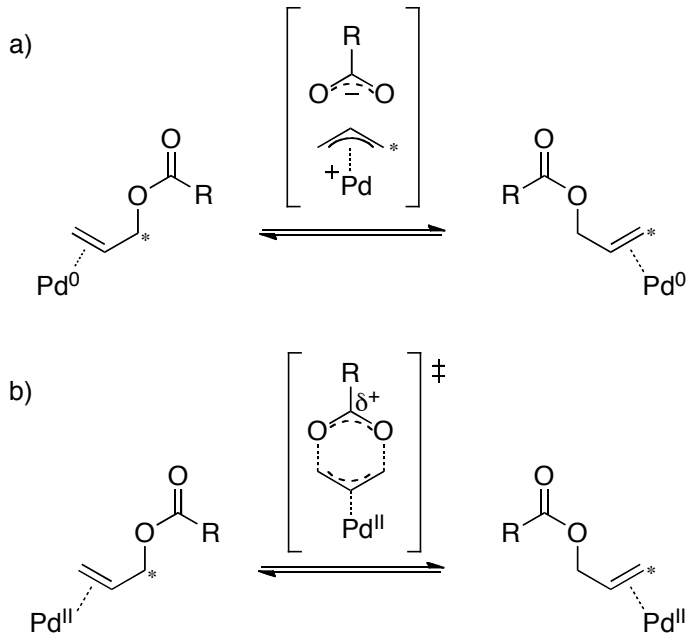
3.3.1 Mechanistic study

We became interested in the mechanism for the isomerization of **3b** and **3c**. The isomerization of allyls has been the object of previous investigations, but mainly concerning stereochemical aspects.[35-38,58] In order to examine whether the return of the leaving group was external (Scheme 17a) or internal (Scheme 17b), a cross-over experiment was performed. Cyclohexenyl carbonate and allyl benzoate were mixed with 2.5 mol% of $Pd_2(dba)_3$ and 5 mol% of P,N-ligand (catalyst **A**). The reaction mixture was analyzed by GC-MS after 70h in order to detect any of the crossover products cyclohexenyl benzoate or allyl carbonate (Scheme 16).



Scheme 16 Cross-over experiment with **3b** and **2c.**

No crossover products were detected, which points to an internal mechanism. The plausible mechanistic explanation for this observation is that benzoate and carbonate groups can stabilize the 1,3-oxo cyclohexenyl cation in the transition state thus pointing to a Pd(II) catalyzed 1,3-migration (Scheme 17b) similar to the Overman rearrangement.[72] The acetate is not able to stabilize the 1,3-oxo cyclohexenyl cation and therefore this process would be expected to be less favorable for acetates, as observed in the isomerization experiment where the acetate did not return to the allyl (entry 4 in Table 2).



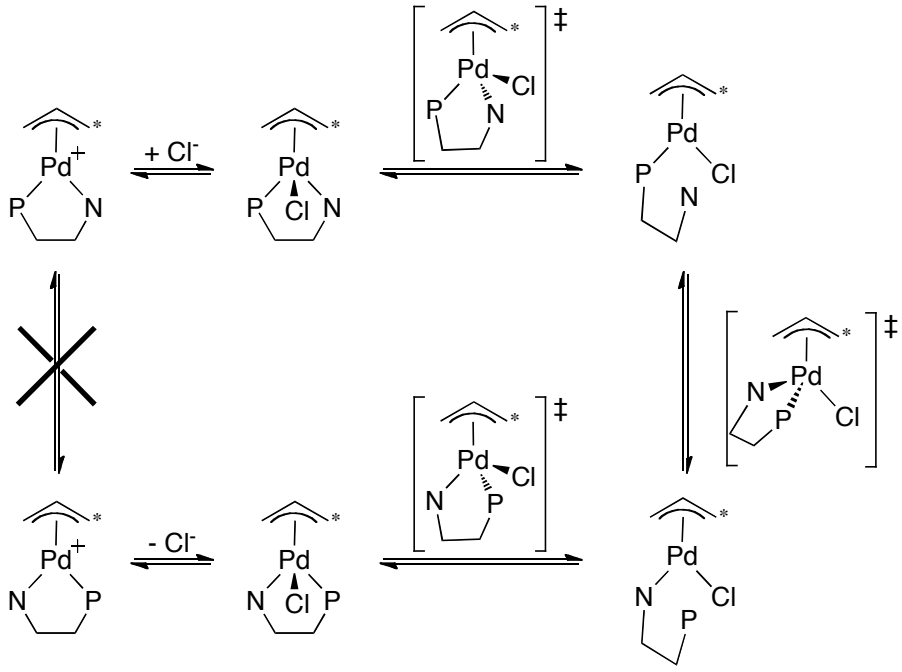
Scheme 17 Plausible mechanisms for the isomerization of allylic substrates: a) Pd(0) assisted pathway, b) Pd(II) assisted pathway.

Since the low regioretention was not a result of isomerization of the allylic substrates, it is most likely a result of dynamic processes in the (η^3-allyl)Pd complexes. Halogens have been shown to increase the rate of the dynamic

processes in (η^3-allyl)Pd complexes by coordination to Pd.[11,12] Even though the reaction was performed under chloride-free conditions, the amount of potentially coordinating anionic ligands, in the form of the leaving group, is increasing as the reaction proceeds. The possible dynamic processes that would lead to a change in the coordinating mode of the ligand, in other words a change from having the labeled position trans to P to a position trans to N, are the apparent rotation of the allyl or the S_N2-type attack by Pd(0) on the allyl. The latter of the two is not likely to be operating since it is slowed down by the use of bidentate ligands and catalytic conditions, *vide supra*.

3.4 Computational results

To confirm that apparent η^3-allyl rotation is a plausible reason for the low observed regioretention in the reaction, a computational study was performed[†]. Surprisingly, the apparent rotation was most likely to proceed via an anion assisted associative-dissociative mechanism as shown in Scheme 18, and not via a T-shaped intermediate[14] *or* pseudorotation[13] as previously reported. This mechanism is supported by the previous observation of an apparent rotation, induced by coordinating solvents or an internal hydroxyl containing tether.[73]



Scheme 18 The proposed mechanism for the anion assisted apparent rotation.

[†] The DFT calculations were performed by Per-Ola Norrby

3.5 Conclusions and outlook

The alkylation of cationic complexes, such as [(η^3-allyl)Pd(P,N-ligand)]$^+$, with malonates shows only a small regioselective memory effect experimentally. The low regioretention observed experimentally was shown, by DFT calculations, to be due to dynamic processes such as apparent rotation, which was induced by anions present in the solution. Also, the regioselectivity turned out to be sensitive to the pre-catalyst used in the reaction.

To continue this project, a study involving nucleophiles that react faster than the apparent rotation of the η^3-allyl would give insight into the true regioretention arising solely from the P,N-ligand (**1**). Examples of fast nucleophiles are Zn-chelated ester enolates, which have been reported by Kazmaier *et al.* to react faster than the rate of η^3-η^1-η^3 isomerization.[63]

4. Regioselectivity in palladium assisted allylic alkylation using complexes with tethered ligands (Papers II, III, IV)

4.1 Introduction and aim

When applying monosubstituted allylic substrates in the palladium mediated allylic alkylation the least hindered, terminal allylic position is favored for substitution. A way to affect the regioselectivity is to use ligands containing donor atoms with different electronic properties (*e.g.* the trans effect). Still, to be able to measure the influence from the trans effect and separating it from steric effects is not trivial. In addition, the dynamic processes in the (η^3-allyl)Pd complexes further complicate the situation. To be able to differentiate between the electronic effects and the steric effects, a rigid complex has to be utilized and all the unwanted dynamic processes have to be diminished. This can be achieved by utilizing a tethered ligand/substrate in pre-formed complexes with a known conformation.

In this study, ligands containing an allylic group tethered to an internal coordinating atom were investigated. In the corresponding Pd complexes the coordinating sulphur atom in the tether is always positioned *trans* to the terminal allylic carbon atom. When adding an auxiliary ligand, X, it will always be positioned *trans* to the internal allylic carbon atom (Figure 8). By analyzing the amount of branched versus linear product in the allylation reaction, the selectivity arising from the trans effect from either of the ligands can be evaluated. A large trans effect from the auxiliary ligand would be expected to give result in an excess of the branched product.

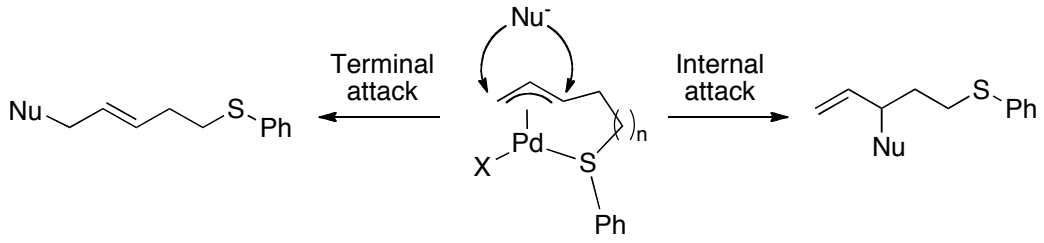


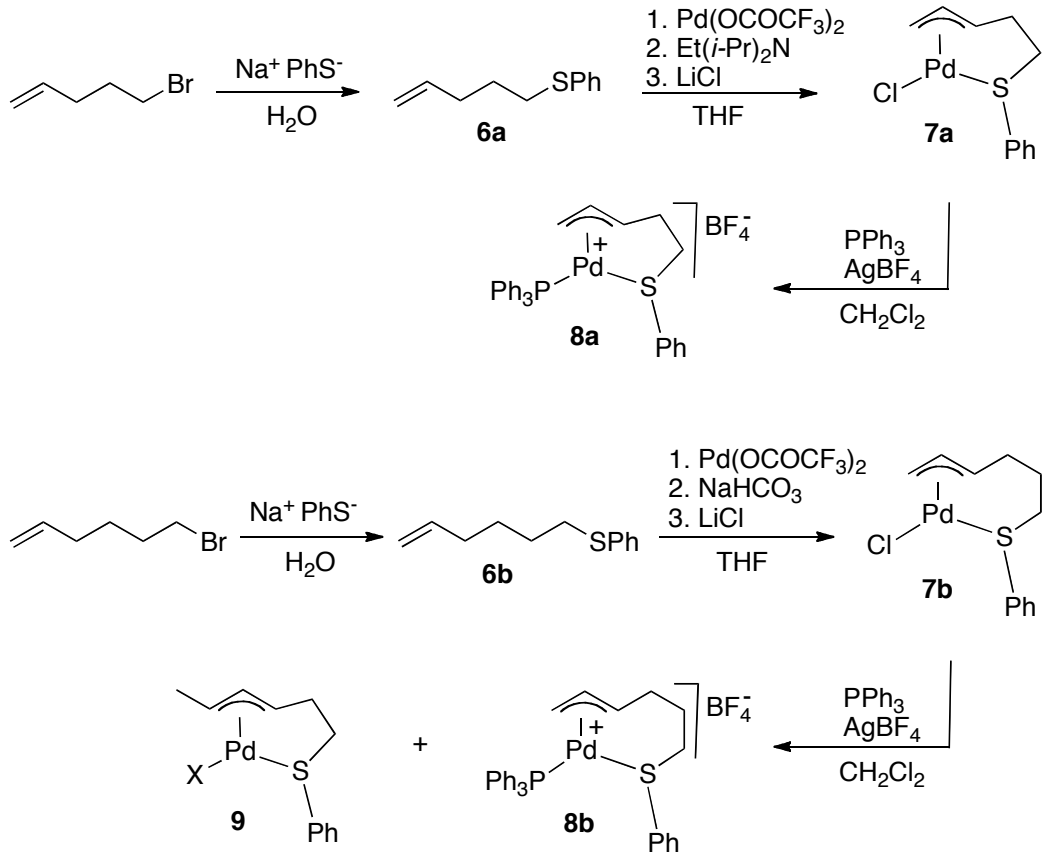
Figure 8 A schematic illustration of the alkylation of the tethered allylic substrate, n = 1 or 2.

Previously, Krafft *et al.* employed the corresponding catalytic systems in their studies.[74,75,76] However, they did not draw any conclusions concerning the trans effect, only reasoned that the tethered ligand may interact with the nucleophile and thereby direct the nucleophilic attack. In this context, this was a plausible

rationalization since this is the expected way of interaction between the nucleophile and the tether in the BPPFA ligands.[55] However to be able to evaluate the trans effect from the two different ligands in the complex, the tether has to be coordinated to Pd during the reaction. Therefore, by performing the reaction using pre-formed Pd-complexes, the coordination of the tether to Pd is ensured. Dynamic processes such as the apparent rotation can be negated by the use of pre-formed tethered complexes. In addition, by performing the reaction with stochiometric amounts of the tethered complexes, any interference from anions in the reaction mixture, *i.e.* OAc and Cl from the substrate and the catalyst respectively, will also be minimized.

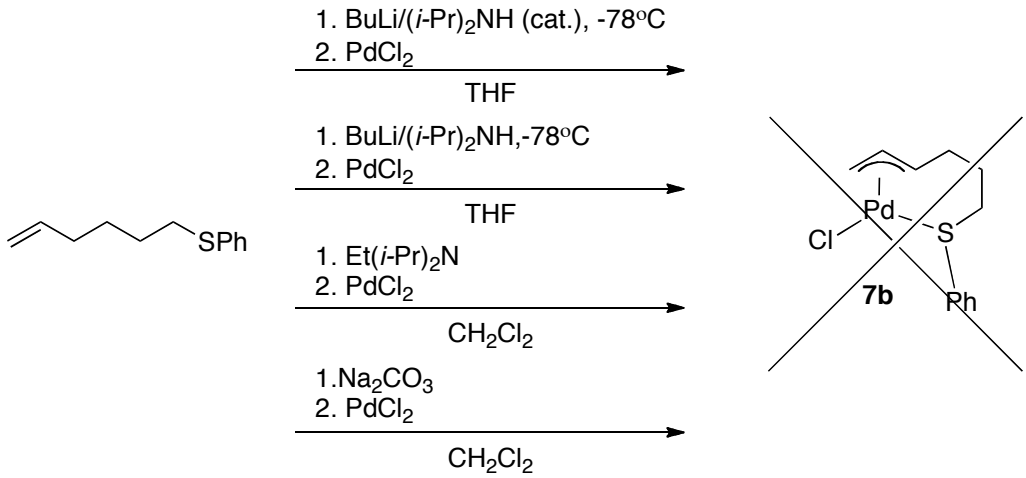
4.1.1 Synthesis

The (η^3-allyl)palladium complexes, **7a-b** and **8a-b**, were synthesized starting from the corresponding bromides according to the synthetic route shown in Scheme 19. The complexes are air stable and were purified by column chromatography followed by crystallization.



Scheme 19 Synthetic route to **7a-b** and **8a-b**.

The thioether precursors (**6a** and **6b**) were prepared in almost quantitative yields (95-98%). Whereas only moderate to low yields were achieved for the complexes **7a** and **7b**, 44% and 29% respectively. However, the corresponding phosphine complexes **8a** and **8b** were isolated in almost quantitative yields, 97% and 98% respectively. When synthesizing the larger complex (**8b**) a regioisomeric by-product, **9**, was formed and made up 10-20% of the crude product. This unfortunately led to difficulties during the purification, since the two products were not separable by column chromatography and frequently co-crystallized. Attempts to synthesize the larger complex by using other methods were made, as depicted in Scheme 20, but unfortunately failed. However, the by-product does not produce the same products as **7b** and **8b** in the allylic alkylation and therefore the mixture of the isomers was applied in the reaction.



Scheme 20 Alternative routes to **7b**.

4.1.2 Structure determination of the complexes

The *syn*- and *anti*-isomers of the (η^3-allyl)Pd complexes have different reactivity and to be able to compare the results from the alkylation of the complexes, it is of importance that they exist in the same isomeric form. Therefore, both 1D- and 2D-^{1}H-NMR spectroscopy and X-ray diffraction spectroscopy[†] were performed on the complexes **7a-b** and **8a-b**.

The ^{1}H-NMR spectra of the complexes were fully assigned by using COSY experiments and the structure was determined by measuring the coupling constants between the protons in the allyl. Primarily, the coupling constant between H2 and H3 is informative for determining whether the complex is the

[†] Crystal structure determinations were performed by Susanne Olsson.

syn- or the *anti*-isomer. In the *anti*-isomer, where the H3 is in *syn* position, the coupling constant is in the range of 6.5-8 Hz, and in the *syn*-isomer, where the H3 is in *anti* position, the coupling constant is in the range of 11.5-14 Hz.[46] In all complexes, **7a-b** and **8a-b**, the coupling constant between H2 and H3 was in the range of 11-13 Hz, which confirmed that all detectable complexes were *syn*-isomers in solution.

The X-ray structures clearly showed that all complexes were *syn*-isomers also in solid phase, as illustrated in Figure 9. In the two complexes with shorter tether (**7a** and **8a**), the carbon C4 is "bent down" due to the coordination of the tethered sulphur atom to Pd.

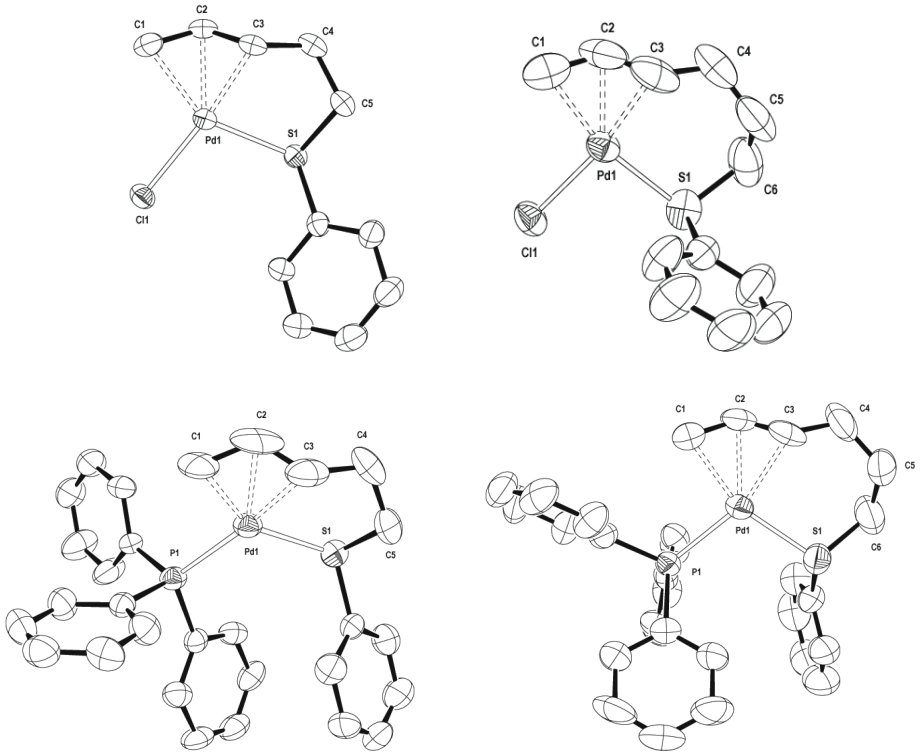
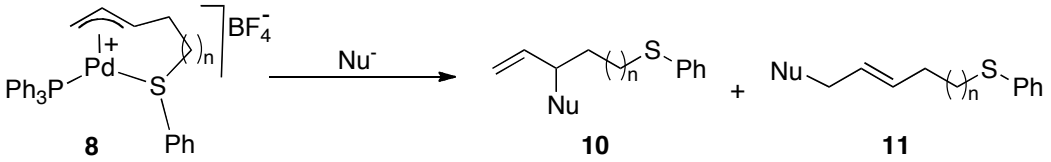


Figure 9 X-ray structure of the neutral complexes **7a** and **7b** (top) and the cationic complexes **8a** and **8b** (bottom), hydrogens are omitted for clarity.

4.2 The role of the tether size on selectivity

Complexes **8a-b** were applied in the allylic alkylation, using sodium dimethyl malonate as the nucleophile (Scheme 21). Analysis by GC and ^{1}H-NMR spectroscopy showed that each complex gave rise to both the branched product, **10a-b**, from the internal attack, and the linear product, **11a-b**, from the terminal

attack. The smaller complex, **8a**, showed a preference for the internal attack, leading to an excess of the branched product. On the other hand, when applying the larger complex, **8b**, a change in product distribution was observed by yielding an excess of the linear product. The results are summarized in Table 3. The product distribution showed similar preference in regioselectivity as the previously reported catalytic system.[74,75,76]



8 **10** **11**

a) n=1, **b**) n=2

Scheme 21 The regioisomeric products from the reaction between **8a-b** and sodium dimethyl malonate.

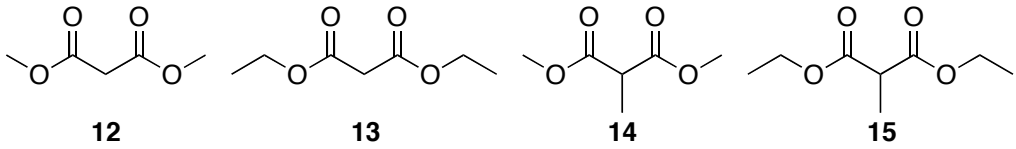
Table 3 Product distribution from the reaction between **8a** or **8b** with sodium dimethyl malonate.

Entry	Complex	Branched, **10** **%**	Linear, **11** **%**
1	**8a**	80	20
2	**8b**	20	80

These experimental findings were not in agreement with the expectation that the trans effect arising from the auxiliary phosphorous ligand would solely determine the product distribution, *vide infra*, which would lead to similar product ratios in both entry 1 and 2 in Table 3.

4.3 The role of the nucleophile on selectivity

As a continuation of the previous study, the influence of size of the nucleophile on the selectivity in the reaction was investigated (Scheme 21). If there is a steric interaction between the substrate and the nucleophile, a small nucleophile would be able to give a higher ratio of branched product than a larger nucleophile. Four different malonates were chosen for the study (Figure 10). When applying the five-membered complex, there was only a minor change in the selectivity towards the linear product (entries 1-4 in Table 4). When the six-membered complex was applied, a minor change was observed too, but unexpectedly towards the branched product when utilizing larger nucleophiles (entries 5-8 in Table 4).



12 **13** **14** **15**

Figure 10 Structures of the malonates utilized in the study.

Table 4 Product distribution from the reaction between **8a** or **8b** with different nucleophiles.

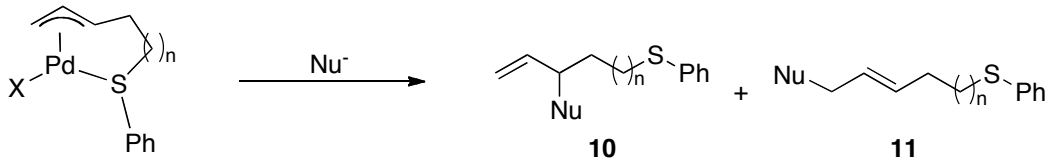
Entry	Complex	Nucleophile	Branched **%**	Linear **%**
1	**8a**	**12**	80	20
2	**8a**	**13**	77	23
3	**8a**	**14**	76	24
4	**8a**	**15**	78	22
5	**8b**	**12**	20	80
6	**8b**	**13**	20	80
7	**8b**	**14**	25	75
8	**8b**	**15**	25	75

4.4 The role of the auxiliary ligand on selectivity

Since both chloride and nitrogen ligands are known to induce less trans effect than phosphines,[77] we wanted to see whether the amount of terminal attack would increase when using chloride or pyridine as external ligands (Scheme 22). Further, by employing an excess of PPh_3 or the bidentate phosphorous ligand dppe, we believed that the tethered sulfur ligand would be displaced by the phosphorous ligand and thereby no selectivity arising from the ligands would be achieved.[†] As expected, when using either chloride or pyridine as auxiliary ligands, the amount of branched product was reduced compared to when using PPh_3, for the smaller complexes (n=1). Furthermore, when employing dppe a large shift in selectivity was observed, producing mainly the linear product arising from the attack at the less hindered terminal allylic terminus. This latter result definitely rules out that the sulfur tether directs the nucleophile to internal attack as previously suggested by Krafft *et al.*[75] When using an excess PPh_3 a similar ratio between the products as that when using dppe is observed. The larger complexes (n=2) did not show much difference in product distribution

[†] In those experiments, mainly the five membered complexes were used, due to difficulties in the isolation and purification of the six membered complexes.

when using PPh_3 or Cl as auxiliary ligands. The results are summarized in Table 5.



a) n=1, **b**) n=2

Scheme 22 The regioisomeric products from the reaction of complexes with different auxiliary ligands, X, with sodium dimethyl malonate.

Table 5 Product distribution from the reaction between complexes with different auxiliary ligands, X, and sodium dimethyl malonate

Entry	Tether n	Auxiliary ligand X	Branched, **10** %	Linear, **11** %
1	n = 1	PPh_3	80	20
2	n = 1	Cl	60-65	35-40
3	n = 1	Pyridine	55-60	40-45
4	n = 1	dppe	5	95
5	n = 1	PPh_3 (4 eq.)	7	93
6	n = 2	PPh_3	20	80
7	n = 2	Cl	20	80

4.5 The correlation between Pd-C bond length and reactivity

By measuring the Pd-C bond lengths in the allylic moiety, it is possible to gain information about the electronic influences from the ligands (*i.e.* the trans influence). We wanted to see whether there was any correlation between the Pd-C bond lengths and the reactivity of the allylic positions. There have been reports that the longest Pd-C bond in the allyl moiety is the more reactive.[78,79]

The Pd-C bond lengths were measured in the X-ray structures and compared with the reactivity for the different positions in the allyl moiety. Starting with the two smaller complexes, **7a** and **8a**, an interesting observation was made in complex, **7a**, where the preferred nucleophilic attack was on the allylic carbon atom with the shortest Pd-C bond (entry 2, Table 5). In complex **8a** the terminal Pd-C bond and the internal Pd-C bond in the allyl had almost of the same length, 2.156 and 2.155 Å, respectively. Still, a preferred nucleophilic attack at the internal carbon atom was observed (entry 1, Table 5). In complexes **7b** and **8b**, the only

observation of a preferred nucleophilic attack on an allylic carbon atom with the longest Pd-C bond was found in complex **7b**, where a terminal attack was preferred (entry 7, Table 5). **8b** was the only complex where the longest bond was trans to the donor atom with the expected stronger trans influence (P), but still the preferred nucleophilic attack was at the other, terminal, carbon atom (entry 6, Table 5). The results are summarized in Figure 11.

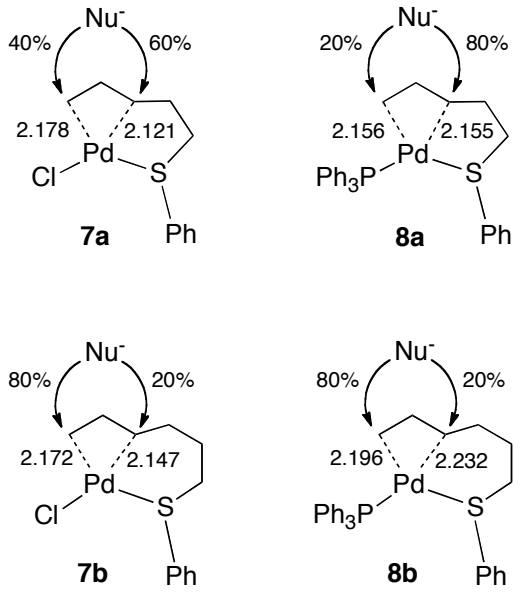


Figure 11 Comparison between Pd-C(allyl) bond lengths and regioselectivity. Bond lengths in Å.

In this study, no direct correlation between the Pd-C bond lengths in the allylic moiety and the reactivity of the allylic positions could be established. This was clearly an example of when the trans effect and the trans influence not are correlated, since the longest bond was not the more reactive in the complexes **7a**, **8a** and **8b**.

4.6 Computational results

A computational study was performed[†] in order to see if the experimental and X-ray results could be verified with calculations and also to gain a better understanding on why the shift in preference occurs when increasing the tether length of the substrate. First, the corresponding *syn*- and *anti*-isomers of the complexes were compared and the results confirmed that the *syn*-isomers of both complexes were much lower in energy than the corresponding *anti*-isomers, which is in agreement with the experimental findings. The *anti*-isomers were

[†] The DFT calculations were performed by Jonatan Kleimark.

significantly higher in energy, which decreases the possibility of having *anti*-isomers of the complexes. However, the reaction itself could still proceed via the *anti*-isomers, due to the Halpern effect.[80,81] The calculations showed that the transition states for the *anti*-isomers were also very high in energy which concludes that the *anti*-isomers are not participating in the reaction. Secondly, the study revealed that steric interactions from the methylene group adjacent to the allyl in the larger complex **8b**, hindered the nucleophile to attack at the internal carbon in the allylic moiety (Figure 12). The steric interaction from the methylene group may appear to be small, but it seems to have a large impact on the selectivity since it outcompetes the trans effect from the phosphorous ligand.

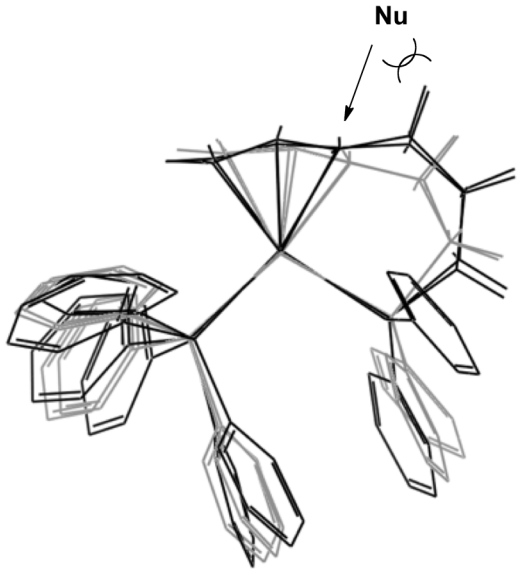


Figure 12 An overlay of the two complexes (**8a** in grey and **8b** in black), showing the steric interactions between the larger complex and an incoming nucleophile. Phenyl hydrogens are omitted for clarity. (The figure was kindly provided by Jonatan Kleimark.)

4.7 Conclusions and outlook

The steric interactions appear to have the strongest influence on the regioselective outcome in the reaction of the studied complexes. However, a selectivity arising from the trans effect from the PPh_3 ligand could be observed when reducing the steric interactions from the tether, as seen for the smaller complexes (**7a** and **8a**). However, no correlation between the observed Pd-C bond lengths in the solid state (trans influence) and the reactivity of the different allylic carbon atoms could be found.

The experimental findings concerning the regioselectivity when using larger nucleophiles and also the lack of correlation between the Pd-C bond lengths and reactivity of the allylic positions, need to be complemented with a computational study to be fully explained.

5. The Tsuji-Trost reaction as a quantitative probe for trans effect from pyridines (Paper V)

5.1 Introduction and aim

The trans effect has an important influence on the ligand induced selectivity in allylic alkylations. Therefore, to be able to compare different electronic effects from the ligands is an important task in the developement of new, selective ligands for the reaction.[82]

An elegant way of using the change in trans effect is presented in the study by Pfaltz *et al*. on regioselectivity induced by phosphinooxazoline (PHOX) ligands, where they saw an increased selectivity, arising from nucleophilic attack trans to the phosphorous atom in the ligand, when shifting from PPh_2 to the more electron withdrawing $P(C_6F_5)_2$.[83] A study on the correlation between the Hammett σ-values for the aromatic substituents and the stereoselectivity arising from PHOX ligands has been reported for the allylic alkylation reaction.[84] However, since the substituents (X) are positioned in a conjugated part of the ligand the effect might be spread out between the two donor atoms (P, N) in the ligand (Figure 13). This can be avoided by applying auxiliary ligands containing different substituents.

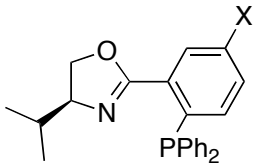


Figure 13 The substituted PHOX ligands.

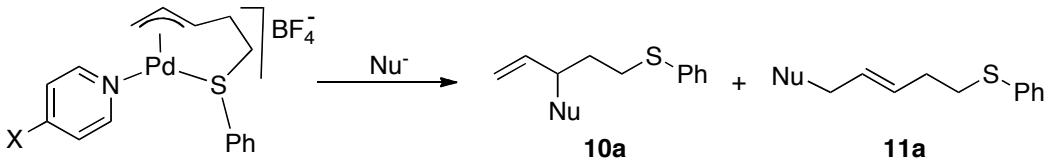
Computational studies have shown a decreased trans effect from the pyridine ligand when going to more electron donating substituents, in complexes with pyridine and phosphine ligands.[78,85] However, the regioselectivity was shown to also be dependent on whether the reaction proceed via an early or late transition state.[85]

The aim with this study was to see whether there were any changes in the regioselectivity in the reaction depicted in Scheme 23, when using different para-substituted pyridines as the auxiliary ligands. Further, the possibility to quantify the trans effect from the different pyridines was investigated. The basic idea was that a correlation between the product distribution and the Hammett σ-values for the substituents would be able to provide a quantitative value of the trans effect induced by the different pyridine ligands. For the study, the five-membered

complex (**7a**) was chosen since the previously described outcome in the allylic alkylation when applying pyridine as an auxiliary ligand gave a product ratio of approximately 55:45. In competitive studies it is desirable to have an approximate product ratio of 50:50 when applying the non-substituted substrate.

5.2 Results

Six pyridines, the non-substituted and pyridines with either electron donating (NMe_2, OMe, Me) or withdrawing (COOMe, CF_3) substituents, were applied as auxiliary ligands in the allylic alkylation reaction, as depicted in Scheme 23.



Scheme 23 The regioisomeric products from the reaction between complexes with different substituted (X) pyridine ligands, and sodium dimethyl malonate.

Attempts to isolate the pyridine complexes prior to the reaction often led to decomposition of the complexes or the complexes failed to crystallize. Therefore, the experiments were carried out *in situ* by first adding $AgBF_4$ and the pyridine derivate to the Pd-complex (**7a**) in CH_2Cl_2, and thereafter adding the nucleophile. The results in the alkylation reactions showed a small preference for terminal nucleophilic attack, giving the linear product (**11a**), when going to more electron donating substituents on the pyridines (*i.e.* decreasing trans effect from the pyridines), Table 6. These observations were in correlation with the computational study by Goldfuss.[85]

Table 6 Product distribution, depending on the pyridine substituents, in the alkylation reaction using sodium dimethyl malonate.

Entry	Substituent X	σ-value	Branched, **10a** %	Linear, **11a** %
1	NMe_2	-0.81	44-46	54-56
2	OMe	-0.27	50-53	47-50
4	Me	-0.17	50-51	49-50
3	H	0	56-59	41-44
5	COOMe	0.45	52-62	38-48
6	CF_3	0.54	54-59	41-46

In Chart 1, the logarithmic relative rates of formation of the two products (**10a** and **11a**) are plotted against the Hammett σ–values[86]. However, the application of pyridine ligands with electron withdrawing substituents unfortunally gave very varying results in the alkylation reaction (entries 5-6, Table 6). Therefore, no complete Hammett correlation could be created for the different pyridine ligands. Thus, it is possible to detect a trend for the electron donating substituents (solid line, Chart 1) in the Hammett plot from the competitive study. Although the results were too preliminary to give any exact information of the substituent effect, a trend can be observed by a positive ρ-value (*aprox.* 0.3). Namely, that the reaction occures faster at an allylic carbon atom situated trans to a ligand with more electron withdrawing capability.

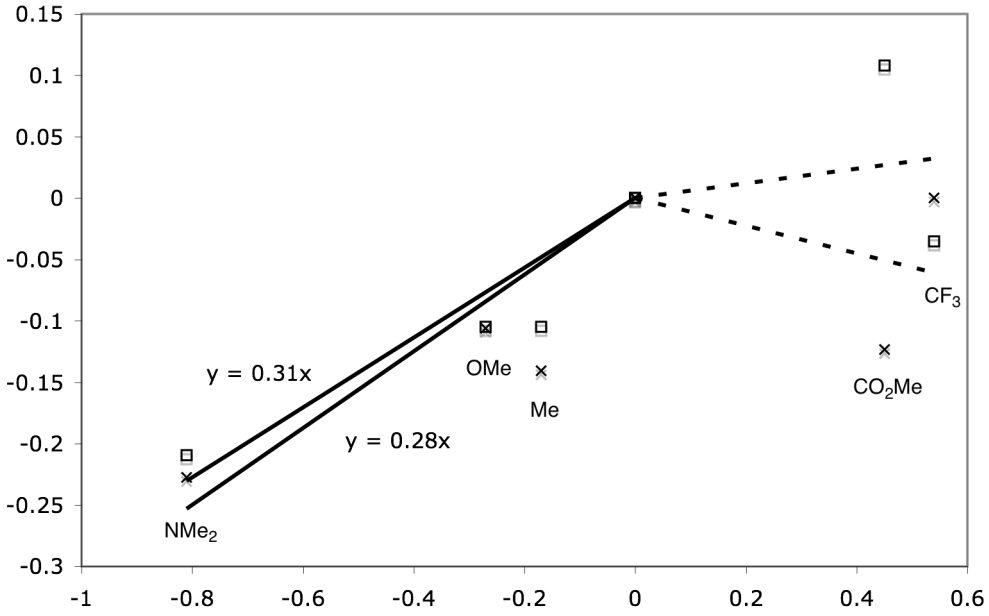


Chart 1 The relative rates of formation of the products **10** and **11**, plotted against the Hammett σ–values.
Solid line = electron donating substituents, dashed line = electron withdrawing substituents.

5.3 Conclusions and outlook

A small change in the regioselectivity could be achieved by changing the substituents on the auxiliary pyridine ligand, hence changing the trans effect. The trans effect is a result of two modes of interaction between the metal and the ligand. First the σ-donation from the ligand to the metal, and secondly the π-

donation from the metal to the ligand (back-bonding). Nitrogen ligands are usually good σ-donators but poor π-acceptors. With electron donating substituents on the nitrogen ligand, the σ-donor ability should increase, which in turn increases the trans effect. However, the opposite was observed in this study. Although, this is not an improbability since the electron pair on nitrogen is not participating in the aromatic system. On the other hand, the π-accepting ability would increase with electron withdrawing substituents and thus increasing the trans effect from the ligand. This has been observed for phosphine ligands.[83] A conclusion to these observations would be that in this system the π-accepting capability of the ligand is the main component in the resulting trans effect. This is in agreement with the observations of accelerating reaction rate when using π-accepting ligands.[32]

The system has a potential to be used as a probe in studying the trans effect from the auxiliary ligand. However, more work needs to be done in the project before this probing system can be utilized properly. The outcome in the reaction when using the ester-substituent on the pyridine was very varying. For further investigations, the electron withdrawing nitro-substituent might be used instead of the ester.

In the previously reported study on the PHOX ligands, a larger difference in selectivity between the ligands was observed when benzyl amine was used as nucleophile instead of sodium dimethyl malonate.[84] It would be interesting to see whether there would be any changes in the selectivity when applying benzyl amine in this pyridine study.

6. Summary and outlook

It is of great importance to be able to understand the underlying mechanisms in a reaction to be able to predict the outcome of the final product, for example when designing new selective ligands for the reaction. The area of palladium mediated allylic alkylation has been the object of numerous investigations. However, the underlying motives on the selectivity in the reaction are still not completely understood. The results presented in this thesis have answered some of the questions, but at the same time given rise to new questions.

In the study on regioselective memory effects, arising from the nucleophilic attack on the allylic moiety trans to phosphorous in the coordinating ligand, the alkylation of cationic [(η^3-allyl)Pd(P,N-ligand)]$^+$ complexes only showed a small regioretention experimentally. This can be compared to the relatively large observed regioretention reported for neutral complexes.[64] The low regioretention could be explained by the apparent rotation of the allylic moiety. In turn the apparent rotation was shown to proceed via an anion-assisted mechanism. As a continuation to this project, the application of nucleophiles that react faster than the apparent rotation would give information on the regioretention arising from the P,N-ligand.

By studying the product distribution in the reaction of (η^3-allyl)Pd complexes containing a tethered ligand, it was shown that the attack of the nucleophile is sensitive to steric interactions from the substrate. However, by increasing the size of the nucleophile only a small change in the product distribution could be observed. A complementary computational study would be able to give more information on the selectivity determining mechanisms in the reaction.

The (η^3-allyl)Pd complexes containing a tethered ligand were analyzed both in solid state and in solution. Thereafter a comparison between the Pd-C bond lengths in the allylic moiety and the reactivity was made by analyzing the product ratio in the reactions. However, no direct correlation could be established for the different complexes in the study. This is contradictory to previous reports on the longest Pd-C bond being the more reactive.[78,79]

A probe for analyzing the trans effect from auxiliary ligands were developed and applied in the analysis of *para*-substituted pyridine derivates. The preliminary results showed a decrease in the nucleophilic attack trans to the auxiliary ligand when going to more electron donating substituents on the pyridine. This indicates that it is mainly the ligands π-accepting ability that determines the regioselectivity of the nucleophilic attack in palladium mediated allylic

alkylation. However, the results when applying derivates with electron withdrawing substituents were very varying. Therefore, more work needs to be done in this project before the probe can be utilized properly.

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