Palladium and rhodium allyl complexes in catalysis
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Chapter 2
Chapter 2
Palladium catalyzed allylic alkylation
(introduction to chapters 3-9)

2.1 Introduction

\[
\text{Figure 1: Palladium catalyzed allylic alkylation using allyl acetate and sodium diethyl 2-methylmalonate as the nucleophile.}
\]

The allylic alkylation reaction (figure 1), first discovered by Tsuji\cite{1} and its enantioselective variant, later developed by Trost and others,\cite{2,3} has become a powerful and versatile tool in synthetic organic chemistry. The reaction allows for a variety of allylic substrates as well as a variety of nucleophiles. An example of an application of the allylic substitution in the total synthesis of the alkaloid (+)-γ-lycorane is shown in figure 2.\cite{3c}

\[
\text{Figure 2: Use of the allylic substitution for the synthesis of (+)-γ-lycorane.}\cite{3c}
\]

Although initially palladium was used for this reaction, it now appears that virtually every metal capable of binding to an allylic substrate can be used.\cite{4} This reaction has become one of the standard reactions for testing new chiral ligands. To obtain a high enantioselectivity, there seem to be no restrictions concerning either the type and number of ligand donor atoms or the type and size of substituents on the ligand. Because of the high reaction rates and high yields, palladium is still the metal of choice in most cases. The use of
other metals may be desirable for certain substrates, since it may lead to selectivities different from those found for palladium\textsuperscript{[4]}. As mentioned in chapter 1, our studies will focus on palladium.

2.2 Enantioselectivity

A vast amount of studies has been published, reporting the use of many different kinds of ligands for the enantioselective alkylation of various substrates (figure 3). Most often substrates are used with large substituents, such as two phenyl rings. Because ligands having completely different electronic and steric properties show similar (high) enantioselectivities,\textsuperscript{[2, 3]} the substitution pattern on the allyl moiety seems to be the most important factor determining the enantioselectivity of the reaction. Much less studies are known, concerning the use of smaller substrates. Smaller substituents on the allyl moiety lead to less steric interaction between the ligand and the allyl group and consequently to a less efficient transfer of chiral information. For such substrates, therefore, only ligands bearing the chiral center in close proximity to the metal center have been successful\textsuperscript{[2a, 5]}.

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{allylic-substrates.png}
\caption{Several allylic substrates often used as models in the enantioselective allylic alkylation.}
\end{figure}

\textit{Steric models}

Several years ago, Trost has presented a model for the mechanism of the chiral induction in the allylic alkylation (figure 4).\textsuperscript{[2]} The model explains the observed enantioselectivities in terms of steric hindrance. Trost proposed that the main factor influencing the outcome of the reaction is the steric interaction between the ligand and the substituents on the allyl group. Upon nucleophilic attack, the substituents will have to bend in the direction of the Pd(ligand) fragment, giving rise to steric interactions. During the formation of the new carbon-carbon bond, the allyl moiety rotates to form the olefin product. Upon rotation, the substituents on the allyl and the (former) nucleophile interact with the Pd(ligand) fragment. The resulting selectivity depends on the relative contributions of the various steric interactions. The model has proven to be very useful in the explanation of many enantioselectivity studies.\textsuperscript{[2, 3, 5]}
2.3 Regioselectivity

Considerably less has been reported concerning the enantioselective alkylation of substrates that lead to intermediate palladium complexes bearing a non-symmetrically substituted allyl moiety.\textsuperscript{[14]} To obtain a high enantioselectivity, regioselectivity is required in addition to enantiocontrol (figure 5). Attack on the non substituted C1 atom in figure 5b leads to the formation of the non chiral linear product, whereas attack on the substituted C3 atom leads to the chiral branched product. For most ligands the formation of the linear product is highly favored over that of the chiral branched product.\textsuperscript{[6]} Although the use of other metals such as molybdenum\textsuperscript{[4]} or rhodium\textsuperscript{[4]} may lead to 99\% selective formation of the branched product, palladium still offers the advantage of a higher reaction rate, higher yield and a large tolerance for many functional groups.\textsuperscript{[2]}

Figure 5: Regioselectivity in the palladium catalyzed allylic alkylation: a): enantiocontrol, b): regiocontrol prior to enantiocontrol.
Several methods are known to influence the regioselectivity of the reaction. In some cases, the nucleophile can be forced to attack on the branched position by modifying the allylic substrate in such a way that attack on the branched position is favored for geometric reasons. An example is presented in figure 6, in which the nucleophilic attack occurs intramolecularly. The preference for the formation of a six-membered ring compared to an eighth-membered ring.

Another method involves the use of bidentate ligands bearing two different donor atoms. Extensive NMR studies by Pregosin have shown, that apart from steric interactions, the regioselectivity of the nucleophilic attack is for a large part determined by the different trans influences of the ligand donor atoms. Using bidentate P-N or P-S ligands, the nucleophile primarily attacks the allylic carbon atom trans to the phosphorus.

\[
\text{Ligand} = \begin{array}{c}
\text{(dba)}_3\text{Pd}_2\text{CHCl}_3 \\
\text{Ligand} = \text{THF} \\
\text{Pd-Ligand}
\end{array}
\]

Figure 6: Internal alkylation of pro-branched allylic substrate.

Memory effect

\[
\begin{array}{c}
a \quad \text{Nuc} \\
\text{OAc}^\ominus \\
b \quad \text{Nuc} \\
\text{OAc}^\ominus
\end{array}
\]

Figure 7: Illustration of the "memory effect" in the alkylation of a dimethyl substituted allyl moiety.

In recent years several studies have been devoted to the so-called "memory effect". In some cases, it has been found, that the nucleophile shows a preference for attack on the allylic carbon atom, to which the leaving group in the substrate was bonded prior to oxidative addition (figure 7). Thus, although both substrates lead to the formation of the same intermediate Pd(allyl) complex, the use of substrate a mainly yield product a', while use of substrate b leads to b'. Such a "memory effect" was found for monodentate
Palladium catalyzed allylic alkylation (introduction to chapters 3-9).

ligands, but also for some mixed bidentate ligands. Several sophisticated studies have been performed to elucidate the origins of these observations. A number of explanations for this observation has been presented, e.g. involving ion pairs. We, however, propose a simple alternative explanation to account for the observations.

For Pd(monodentate phosphine) complexes, it is known that the oxidative addition of allylic substrates to palladium occurs in a cis fashion. Thus, after oxidative addition of a to Pd-P, initially the complex a-Pd is formed (figure 8), in which the substituted carbon is located cis to the phosphorus ligand. The subsequent nucleophilic attack is known to primarily take place trans to phosphorus and for steric and electronic reasons product a' will be formed as the main product. Using the substrate with the leaving group on the other terminal carbon atom will yield intermediate b. Nucleophilic attack trans to phosphorus yields the other regio-isomer, b'. It is known that the intermediate b-Pd, bearing the substituent on the allyl moiety trans to phosphorus, is thermodynamically more stable than intermediate a-Pd (chapter 6). The overall regioselectivity of the reaction therefore is determined by the rate of a-Pd \(\leftrightarrow\) b-Pd isomerization, the a-Pd / b-Pd equilibrium value and the rate of alkylation for the two isomers. Thus, the "memory effect" can be explained by kinetic versus thermodynamic control of the regioselectivity of the reaction (figure 8).

The a-Pd \(\leftrightarrow\) b-Pd isomerization is known to be dependent on the coordinating abilities of the counterion and consequently also on the solvent (chapter 6), which explains the observed effects of solvent and counterion on the "strength" of the "memory effect".

Figure 8: A possible, simple explanation for the "memory effect". L is a phosphine ligand.
2.4 Modeling studies

With the increasing availability of cheaper CPU-time and the demand for better mechanistic insights, high level modeling studies are increasingly used to help the elucidation of reaction mechanisms. In recent years, a large number of theoretical studies dealing with the nucleophilic attack on Pd(η^3-allyl) complexes has appeared.\[^{111}\]

The accuracy of these calculations, however, are hampered by the electrostatic attraction between the negatively charged nucleophile and the positively charged palladium atom. Because the interaction between charged molecules is ill described in the gas phase, the neutral ammonia nucleophile is often used as a model. Solvent models can be used to diminish the electrostatic interactions between palladium and the nucleophile, but this requires many extra calculations. To date, no fully conclusive calculations concerning the regioselectivity of the alkylation have been reported.\[^{114d}\]

The modeling studies reported so far, have confirmed some of the features of the model presented by Trost. Upon nucleophilic attack of NH\(_3\), the allyl moiety rotates in such a way that the newly formed C=C double bond will be in the Pd(ligand) plane. Following the reaction at low temperature by means of NMR spectroscopy, such olefin complexes have indeed been observed.\[^{114i}\] The reaction is essentially controlled by the frontier orbitals, but the overall results are the same as predicted by a purely steric model. Because the used theoretical models lack large steric groups, the full steric implications of the "Trost"-model have not been evaluated yet.

Extrapolation of details of these calculations to the alkylation reaction is questionable. Åkermark has investigated experimentally the influence of the strength of the nucleophile on the regioselectivity.\[^{112}\] It was found that for relatively hard nucleophiles, such as malonate, electronic factors are more important for the regioselectivity than they are for less reactive, softer nucleophiles. An extrapolation of calculations for attack of ammonia will thus underestimate the contribution of electronic factors.

In conclusion, although the steric model and the theoretical studies can explain some features of the regioselectivity, the predictions are valid only for certain nucleophiles, certain allyl moieties and certain ligands. We will show that these explanations fail for some borderline cases.
2.5 Scope and content of the chapters on allylic alkylation

In the next chapters (3-9), the factors governing the regioselectivity of the palladium catalyzed allylic alkylation will be studied in more detail. First (chapter 3), the mentioned reported modeling studies are discussed in more detail and new calculations are presented that apply directly to the complexes used in the following chapters. In the experimental chapters, the regioselectivity is studied systematically using several series of ligands and a series of allylic substrates. Since preliminary studies in our laboratories had yielded promising results, we chose to focus on the influence of the bite angle of bidentate ligands. In the first experimental chapter (chapter 4), we study the relation between the influence of the bite angle on the structure of palladium complexes bearing the monosubstituted crotyl moiety (3-CH3-C3H4) and the regioselectivity in the allylic alkylation. Using the findings of chapter 4, the alkylation of cis- and trans-substrates is investigated in more detail in chapter 5. The influence of two different donor atoms (P-N) on the alkylation of crotyl and cinnamyl moieties (3-Ph-C3H4) is studied in chapter 6. A detailed investigation of the effect of the bite angle on the bond between palladium and a disubstituted allyl moiety (3,3-(CH3)2-C3H4) is presented in chapter 7. The last experimental chapter, chapter 8, deals with the influence of different donor atoms in a series of ligands based on the xanthene backbone. Finally, in chapter 9, the results of the allylic alkylation are evaluated and a model is presented that accounts for all our observations.

2.6 References


