Palladium and rhodium allyl complexes in catalysis

van Haaren, R.J.

Citation for published version (APA):
Chapter 9
Allylic alkylation: an evaluation.

9.1 Introduction

In chapter 2 we argued that the late transition state model as described by Trost, although useful in most cases, fails to explain some of the reported regioselectivities. An early transition state mechanism may be a more useful alternative in those cases. In chapter 3, it was shown by DFT studies that both the hydrocarbyl substitution of the allyl moiety and a larger bite angle of the ligand enhance the electrophilicity of the allyl. For substituted allyl groups, the same factors cause a distortion of the Pd-($\eta^3$-allyl) bond to $\eta^1$-$\eta^2$, thereby increasing the regioselectivity for attack on the substituted allylic carbon atom C3 (figure 1), leading to the branched product. In chapters 4-8 we studied the influence of several parameters on the regioselectivity in the allylic alkylation.

![Figure 1: Numbering scheme.](image)

In this chapter, an overview of the results is presented, followed by an evaluation of both the early and the late transition state mechanisms. Finally, a model is presented that accounts for our experimental results. Based on the modeling results (chapter 3) we reasoned that, if the regioselectivity is determined by an early transition state mechanism, alkylation of all substituted allyl moieties studied in chapter 3 will lead to a significant percentage of the branched product. A relatively high selectivity was expected for the dimethyl substituted allyl. Use of P-N ligands was expected to enhance the regioselectivity. Based on the calculated structures, the relative regioselectivity arising from the syn and the anti crotyl moieties was hard to predict. If the non-symmetry of the syn-isomer would be as pronounced as suggested by the DFT calculations, the regioselectivity for the branched product on alkylation of the syn-isomer could be higher. If, however, the calculated partial sp$^3$ hybridization on C3 of the anti-isomer would be important for the regioselectivity, the regioselectivity could be higher for the anti-isomer.
9.2 Overview of alkylation results

Based on the results of the allylic alkylation experiments several parameters influencing the regioselectivity have been identified. A summary of these parameters and their effect on the regioselectivity is presented in table 1.

Table 1: Overview of the parameters influencing the regioselectivity of the palladium catalyzed allylic alkylation (chapter 4-8).

<table>
<thead>
<tr>
<th>Parameter</th>
<th>see chapter</th>
<th>Linear product (example)</th>
<th>Branched product (example)</th>
<th>origin of effect</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Allyl parameters</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>Size of the syn-substituent on allyl moiety</td>
<td>5</td>
<td>large ((\text{C}_3\text{H}_7))</td>
<td>small ((\text{CH}_3))</td>
</tr>
<tr>
<td>2</td>
<td>Number of substituents</td>
<td>7</td>
<td>1 (crotyl)</td>
<td>2 (dimethyl allyl)</td>
</tr>
<tr>
<td>3</td>
<td>Mixture of E and Z substrates</td>
<td>5</td>
<td>long reaction time</td>
<td>short reaction time</td>
</tr>
<tr>
<td>4</td>
<td>Orientation of the substituent in mono substituted allyl groups</td>
<td>4 and 5</td>
<td>syn</td>
<td>anti</td>
</tr>
<tr>
<td>5</td>
<td>Leaving group can coordinate to Pd (dissymmetric ligands)</td>
<td>6</td>
<td>no (OTFA)</td>
<td>yes (Cl)</td>
</tr>
<tr>
<td>6</td>
<td>Leaving group can coordinate to Pd (symmetric ligands)</td>
<td>4, 5, 6</td>
<td>yes (OAc)</td>
<td>no (OTf)</td>
</tr>
</tbody>
</table>
Table 1 (continued): Overview of the parameters influencing the regioselectivity of the palladium catalyzed allylic alkylation (chapter 4-8).

<table>
<thead>
<tr>
<th>Parameter</th>
<th>see chapter</th>
<th>Linear product favored if (example)</th>
<th>Branched product favored if (example)</th>
<th>nature of effect</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Ligand parameters</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>( \pi )-acceptor capabilities of donor atoms (both are the same)</td>
<td>8</td>
<td>small (N)</td>
<td>large (P)</td>
</tr>
<tr>
<td>8</td>
<td>Symmetry of the ligand with respect to the donor atoms</td>
<td>6</td>
<td>P-P</td>
<td>P-N</td>
</tr>
<tr>
<td>9</td>
<td>Position of P in allyl complexes of P-N ligands</td>
<td>6</td>
<td>cis to C3</td>
<td>trans to C3</td>
</tr>
<tr>
<td>10</td>
<td>Bite angle</td>
<td>4-7</td>
<td>small</td>
<td>large</td>
</tr>
<tr>
<td>11</td>
<td>Cone angle, mono substituted syn</td>
<td>4 and 5</td>
<td>large</td>
<td>small</td>
</tr>
<tr>
<td>12</td>
<td>Cone angle, mono-anti and disubstituted</td>
<td>4, 5 and 7</td>
<td>small</td>
<td>large</td>
</tr>
<tr>
<td><strong>Other parameters</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>13</td>
<td>Strength of nucleophile</td>
<td>ref 1</td>
<td>relatively soft</td>
<td>relatively hard</td>
</tr>
</tbody>
</table>

Table 2: Overview of the parameters influencing the reaction rate of the Pd catalyzed allylic alkylation.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>see chapter</th>
<th>slow if (example)</th>
<th>fast if (example)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Allyl parameters</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>14</td>
<td>Size of the syn substituent in mono substituted allyl groups</td>
<td>5</td>
<td>large (( \text{C}_3\text{H}_7 ))</td>
</tr>
<tr>
<td>15</td>
<td>Orientation of the substituent in monosubstituted allyl groups</td>
<td>5</td>
<td>anti</td>
</tr>
<tr>
<td>16</td>
<td>Number of substituents</td>
<td>7</td>
<td>more</td>
</tr>
<tr>
<td>17</td>
<td>Coordinating properties of the leaving group</td>
<td>5</td>
<td>strongly coordinating (OAc)</td>
</tr>
</tbody>
</table>
Table 2 (continued): Overview of the parameters influencing the reaction rate of the Pd catalyzed allylic alkylation.

<table>
<thead>
<tr>
<th>Ligand parameters</th>
<th>18</th>
<th>19</th>
<th>20</th>
</tr>
</thead>
<tbody>
<tr>
<td>18 ( \pi )-acceptor capabilities of donor atoms (both are the same)</td>
<td>8</td>
<td>weak (N)</td>
<td>strong (P)</td>
</tr>
<tr>
<td>19 Bite angle</td>
<td>4-7</td>
<td>small</td>
<td>large</td>
</tr>
<tr>
<td>20 amount of P-donor atoms per Pd</td>
<td>6 and to be published</td>
<td>≠ 2</td>
<td>2</td>
</tr>
</tbody>
</table>

9.3 Evaluation of the early transition state mechanism

The results show that the electronic activation of the allyl moiety is important for the regioselectivity. A clear relation was found between the regioselectivity and parameters as the number of substituents \( (2) \), the \( \pi \)-acceptor capabilities of the donor atoms \( (7) \), the symmetry of the ligand \( (8) \), the orientation of the phosphorus donor atom \( (9) \), the bite angle \( (10) \), the effect of the cone angle for the anti-crotyl and the dimethyl allyl moieties \( ((\text{CH}_3)_2-\text{C}_\text{H}_3) \) \( (12) \) and the strength of the nucleophile \( (13) \).

The effect of a few parameters, however, cannot be explained by the early transition state mechanism. The modeling and X-ray studies (chapter 3, 4, 7) predicted for the syn crotyl moiety an increased distortion of the \( \eta^3 \)-bond to an \( \eta^1 \)-\( \eta^3 \)-bond when the bite angle and / or cone angle is larger \( (11) \). Similarly, the non-symmetry of the Pd-allyl bond was also expected to increase with the size of the syn-substituent \( (1) \). The observed regioselectivities, however, are the opposite of the expected results. An enhanced distortion of the Pd-(syn-R)allyl bond leads to the formation of less branched product.

9.4 Evaluation of the late transition state mechanism

To predict the regioselectivity using the late transition state mechanism is less straightforward than it is for the early transition state mechanism. The model takes into account the steric interactions occurring during the whole process of bond formation. At some point, the steric interactions encountered along the reaction coordinate may conflict, favoring the other regio-isomer.

Nevertheless, some predictions can be made based purely on steric considerations. A lower selectivity for the branched product can be expected for allyl groups carrying more and / or larger substituents. Analogously, an increase of the steric hindrance (large bite and / or cone angle of the ligand) around the palladium would also lead to less branched product.
The results show that the late transition state mechanism indeed accounts for the effect of the cone angle for syn-crotyl (11) and for the effect of the size of the syn-substituent (1). For some of the results, however, it is clear that steric interactions do not play a role. The use of P-N instead of P-P ligands (8), the effect of the cis or trans orientation of the phosphorus in P-N ligands (9), the effect of the bite angle (10) and the strength of the nucleophile (13) are effects that can not be accounted for by the late transition state mechanism.

9.5 Combination of the early and the late transition state mechanisms

The above considerations indicate that neither the early nor the late transition state mechanism satisfactorily explains all observed regioselectivities, showing the limits of these mechanistic models. In general, the former succeeds where the latter fails and vice versa. We have succeeded therefore, in exploring the limits of the early and the late transition state mechanism. A separate explanation of the effect of the different parameters in terms of early or late has a limited utilization, so we attempted to provide an explanation that accounts for all of our results.

Figure 2: Model that accounts for our results, applied to syn and anti crotul. 
The combined model we propose, has been introduced in the previous experimental chapters (figures 2 and 3). Going from the Pd(η³-allyl) complex to the Pd-(olefin-product) complex, the reported modeling studies show no energy minimum (relatively stable intermediate) along the reaction coordinate. Nevertheless, for the sake of argument, we treat the reaction as if it occurs in two stages. In the first stage, the nucleophile approaches the Pd(η³-allyl) complex and selects the most electrophilic carbon atom. During the first stage of bond formation, the attacked carbon gradually changes its hybridization from sp² to sp³. As a result, the substituents on the attacked carbon bend away from the nucleophile, in the direction of the Pd(ligand) fragment. At this point, steric interactions may become important.

After the initial stage, the attacked allyl moiety rotates to form the final Pd(olefin) complex. The site of the attacked carbon atom rotates out of the Pd(ligand) plane, while the site that is not attacked rotates into this plane. The formation of a more substituted double bond and its coordination to palladium are favored for electronic reasons over that of a terminal double bond, so attack on the linear position would be preferred. In contrast, for steric reasons the attack on the branched position may be favored. The rotation of the attacked branched position out of the Pd(ligand) plane decreases the steric interactions, whereas attack on the linear position would lead to a significant increase of steric interaction after rotation of the newly formed substituted double bond into the Pd(ligand) plane.

Summarizing, in the first stage of the reaction, attack on the branched position is favored for electronic reasons and in the second stage it is favored for steric reasons. The opposite applies for attack on the linear position; it is favored in the first stage for steric reasons and in the second stage for electronic reasons.

In the following this mechanism will be used to explain the influence of each parameter mentioned in table 1.
9.6 Evaluation of the combined model

1. Size of the syn-substituent on the allyl moiety (chapter 5).
A larger syn-substituent corresponds to a lower regioselectivity for the branched product. The crystal structures of dimethyl allyl-complexes (chapter 7) show, that the phenyl rings of the ligand are closer to the syn than to the anti methyl substituent. The steric hindrance in the first stage of the reaction therefore, increases with the size of the substituent and the linear product is favored. Apparently, the increase of the steric interactions in the second stage is less important than in the first stage.

2. Number of substituents (chapter 7).
The selectivity for the branched product increases with the number of substituents. Going from C_3H_5 via CH_3-C_3H4 to (CH_3)_2-C_3H_3 leads to a more pronounced distortion of the Pd-allyl bond from η^1 to η^1-η^2 and consequently to an increase of the relative electrophilicity of the C3 atom. The importance of the electronic factors in the first stage is thus enhanced. The increased steric bulk around C3 also leads to an increase of the importance of steric interactions in the second stage. Both effects favor the formation of the branched product.

3. Mixture of E and Z monosubstituted substrates (chapter 5).
In (1:1) mixtures, the Z substrate is alkylated (forming branched and linear product) at a faster rate than the E substrate (forming only the linear product). Therefore, after a short reaction time, the concentration of the branched product is higher than that of the linear product. The situation is reversed after a longer reaction time, i.e. when the Z substrate has been consumed completely.

4. Orientation of the substituent in mono substituted allyl groups (chapters 4 and 5).
The regioselectivity for the branched product is higher for anti complexes than for syn complexes. The modeling studies predicted a more pronounced non-symmetry for the syn substituted allyl moiety, but also a partly sp^3 hybridization on C3 in the anti substituted allyl moiety. The crystal structures (chapter 7) of dimethyl allyl-complexes show, that the phenyl rings of the ligand are closer to the syn than to the anti methyl substituent. The steric interactions in the first stage therefore, are more important for the syn than for the anti substituted allyl moiety. Assuming that the steric and electronic factors in the second stage do not differ much for both isomers, the differences in the first stage determine the regioselectivity.

5. Coordinating properties of the leaving group (dissymmetric ligands) (chapter 6).
The use of chloride as the leaving group leads to a higher selectivity for the branched product when P-N ligands are used. After oxidative addition of the allylic substrate to the Pd^0(ligand) complex, the syn-cis-P allyl complex is formed. The alkylation takes place primarily on the carbon trans to the phosphorus, so the regioselectivity for attack on C1 is high. A coordinating counterion facilitates the isomerization from syn-cis
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-P to syn-trans-P, thereby increasing the probability for attack on C3, leading to the branched product. The steric bulk around the nitrogen functionality is small and the reaction is allowed to follow the electronically preferred pathway.

6. Coordinating properties of the leaving group (symmetric ligands) (chapter 4, 5, 6).
An other effect of the possible coordination of the counterion is its influence on the electron density on the active complex. A long distance of the negatively charged counterion (e.g. triflate) increases the cationic character of the complex and consequently its reactivity towards nucleophilic attack (the electronic factors in the first stage of the reaction). Comparison of the regioselectivity of the stoichiometric and catalytic reactions shows, that for less strongly coordinating counterions (e.g. acetate), a higher selectivity for the branched product is found.

7. The π-acceptor capabilities of donor atoms (symmetric ligands) (chapter 8).
The use of a ligand-donor atom that is a stronger π-acceptor, increases the selectivity for the branched product. The increased π-back donation of the metal to the ligand increases the orbital coefficients in the LUMO (2a") on the allyl moiety, especially on C3. Thus, the electronic factors in the first stage of the reaction are enhanced.

8. Symmetry of the ligand with respect to the donor atoms (chapters 6 and 8)
Going from P-P to P-N the selectivity for the branched product increases. The dissymmetry of the ligand increases the electrophilicity of the allyl and thereby the importance of the electronic factors in the first stage of the reaction.

9. Position of the phosphorus in complexes of P-N ligands (chapter 6)
The electrophilicity of the carbon trans to the phosphorus is larger than that of the carbon cis to phosphorus. A trans orientation of C3 therefore, increases the importance of the electronic factors in the first stage and consequently increases the regioselectivity for the branched product.

10. Bite angle of the ligand (chapters 4-7)
A larger bite angle leads to an increased distortion of the Pd(η^3-allyl) bond and consequently to an enhanced electrophilicity of the allyl. Because of the polarization of the frontier orbitals of the allyl fragment, the effect is more pronounced for C3 than for C1. Thus, the electronic factors in the first stage become more important.

11. The cone angle for monosubstituted syn allyl groups (chapters 4 and 5).
Analogous to the effect of the size of the syn-substituent (parameter 1), the increase of the cone angle increases the steric interactions in the first stage of the reaction, thus decreasing the regioselectivity for the branched product.
12. The cone angle in complexes bearing monosubstituted anti allyl groups and disubstituted allyl groups (chapters 4, 5 and 7).

The increase of the cone angle leads to an increase of the regioselectivity for the branched product. Because of increased steric interactions, the symmetry of the Pd-(\(\eta^3\)-allyl) bond is distorted thereby leading to an enhanced electrophilicity of the allyl moiety. In addition, the steric factors in the second stage increase. Although the steric factors in the first stage increase as well, the electronic effect in the first stage and the steric effect in the second stage are more important.


Åkermark has shown that the use of weaker nucleophiles than sodium diethyl 2-methylmalonate leads to a lower selectivity for the branched product. Although the electronic properties of the allyl are not influenced, they are less important in the first stage of the reaction.

14: Size of the syn substituent in mono-substituted allyl groups (chapter 5).

Larger substituents lead to a lower rate of reaction. This is in line with the above mentioned importance of steric factors in the first stage of the reaction. An increase of the steric interactions naturally decreases the rate of reaction.

15: Orientation of the substituent in monosubstituted allyl groups (chapter 5).

The reaction proceeds faster for E substrates (leading to syn complexes) than for Z substrates (leading to anti complexes), which can be explained by the aforementioned difference in steric effects in the first stage of the reaction.

16: The number of substituents (chapter 7)

Despite a larger electronic activation of the disubstituted allyl moieties compared to monosubstituted allyl moieties, the reaction proceeds at a lower rate. The allylic alkylation leads to a higher regioselectivity for the branched product than found for monosubstituted allyl moieties. Apparently, the increased steric interactions have a strong influence on both the rate and the selectivity of the reaction.

17: Coordinating properties of the leaving group (chapter 5).

A weaker coordination of the counterion to the catalytically active complex decreases the electron density on the complex and consequently on the allyl moiety. Via this way, the reactivity for nucleophilic attack increases and, assuming that the Pd(allyl) complex is not influenced, also the reaction rate will increase.
18: The \( \pi \)-acceptor capabilities of donor atoms (symmetric ligands) (chapter 8).

The reaction proceeds faster for bidentate phosphorus ligands than for ligands with other donor atoms. The rate decreases in the order \( P > As > S > N \). As mentioned above, a stronger \( \pi \)-acceptor enhances the electrophilicity of the allyl and thereby also the rate of the reaction.

19: Bite angle of the ligand (chapters 4-7).

In general, the reaction proceeds faster when the bite angle of the ligand is larger. The increased electrophilicity of the allyl moiety accounts for this observation. For some substrates, however, the rate is slowed down by the increased steric interactions.

20. Number of ligand donor atoms per Pd (chapter 6 and to be published)

Because of the high trans influence and consequently the high electronic activation of the allyl moiety, the highest rates are observed for bidentate phosphine ligands. For two monodentate P-ligands, the rate is lower because of several coordination modes of the ligands (not necessarily cis) and because of the formation of multinuclear Pd-species. A higher L/Pd ratio will lead to the formation of relatively inactive (mononuclear) palladium complexes, from which the excess of ligands have to dissociate before oxidative addition can occur.

9.7 Recent developments

After completion of our studies, several modeling studies of the reaction pathway of nucleophilic attack have been reported.\(^1\) Some studies discuss the regioselectivity of the reaction and the results are in line with the empirical model proposed in this thesis.\(^2\) It is shown that the course of the reaction is controlled by frontier orbital interactions, confirming the observed relation between the distortion of the Pd-allyl and the regioselectivity. The reported studies show, that the orbital interactions and the steric interactions cooperate. Translating these results to our model, the electronic factors in the first stage and the electronic interactions in the second stage favor the same product. Our results suggest, that for some cases, this may not apply. Furthermore, the course of the reaction may be different for nucleophiles that are more reactive than the \( \text{NH}_3 \) group used in the modeling studies.
9.8 Conclusion

We have succeeded in exploring the limits of validity of the existing models for the allylic alkylation. In the experimental chapters 4-8 we have shown that for some cases, neither the late nor the early transition state mechanism satisfactorily explains the results. Our new model, resulting from a combination of the two existing models, covers this undefined area and provides a rationalization for all our results as well as for those of others. Recent theoretical reports support the combined mechanistic model and we are confident that it will continue to be useful in the future.

9.9 References