Chapter 6

Intermolecular Asymmetric Heck Reactions

In this chapter an overview will be given of our efforts to apply phosphoramidites as chiral ligands for intermolecular asymmetric Heck reactions. Phosphoramidites have not been described previously in the literature as suitable ligands for these C-C-bond forming reactions. In the first part of the chapter a short literature overview will be given and in the second part the results of intermolecular Heck reactions with a few ligands will be described. Also a study of a number of reaction parameters that are important with respect to reactivity and enantioselectivity (e.g. solvents and bases) is presented.
Chapter 6

6.1 Introduction

The palladium catalysed arylation of olefins (Heck reaction) is a very powerful method to form C-C bonds.\(^1\) The mechanistic aspects of the Heck reaction are fairly well known, although new details and insights continue to appear.\(^2\) Figure 6.1 shows the general reaction scheme. Of course, the classical (non-chiral) Heck reaction does not produce a stereogenic centre, but as is evident from Figure 6.1, in cases where a \(\beta\) as well as a \(\beta'\)-hydrogen are present in the allyl palladium intermediate 6.2, abstraction of the \(\beta'\)-hydrogen might lead to a newly formed stereocentre.

![Figure 6.1](image)

**Figure 6.1** \(\beta'\)-Hydrogen abstraction in Heck reactions might lead to product 6.3b with a newly formed stereocenter

The general catalytic cycle is believed to proceed according to Scheme 6.1:\(^3\) Oxidative addition of an aryl or vinyl halide or triflate to a Pd\(^0\)-complex (step A) results in a Pd\(^\text{II}\) complex. Coordination of the alkene 6.1 followed by cis-insertion into the Pd-\(R_1\) bond resulting in 6.2 (step B) is followed by \(\beta\) or \(\beta'\)-hydrogen elimination (step C) providing 6.3a or 6.3b. Finally, reductive elimination of HX under influence of base (step D) results in regeneration of the starting Pd\(^0\)-complex.

Of course, regioselectivity depends heavily on the electronic and steric properties of the substituents present in the substrates. The key step regarding enantioselectivity in this reaction is obviously path B, which is dependent on the nature of the chiral ligand used. The nucleophilicity of the counterion (X) also plays a role:\(^4,11b\) If a halide is used the catalytic Pd-complex is neutral. In contrast, if a very weakly coordinating triflate anion is used a cationic Pd-complex is formed, which is considered to provide the pathway with higher stereoselectivity.\(^5\) Addition of silver\(^6\) or thallium salts\(^7\) to a reaction where an aryl halide is used as the aryl source leads to precipitation of the silver or thallium halides, resulting in the cationic Pd-complex, and as a consequence higher enantioselectivities are obtained for a number of examples.
Scheme 6.1  General mechanistic scheme for the (asymmetric) Heck reaction

6.2 Intermolecular Asymmetric Heck Reaction

6.2.1 BINAP as ligand
In 1989 the groups of Shibasaki and Overman reported independently examples of the asymmetric (intramolecular) Heck reaction. Since then, the field of asymmetric intramolecular Heck reaction has expanded rapidly. Results of our efforts will be discussed in Chapter 7.

Hayashi was the first to introduce the intermolecular asymmetric Heck reaction and has since then played a leading role in this area of research. In Scheme 6.2 an intermolecular Heck reaction using PhOTf is illustrated. Treatment of 2,3-dihydrofuran with a number of aryl and alkenyl triflates in the presence of a base (Et₃N or Hunig’s base) and a catalyst, prepared in situ from (R)-BINAP and Pd(OAc)₂, resulted in the formation of (R)-2-aryl-2,3-dihydrofuran and (S)-2-aryl-2,5-dihydrofuran. The major regioisomer formed is always (R)-6.5 (>90%) and ee’s using phenyl triflate exceeded 96% e.e. for (R)-6.5. Usually the ee’s for (S)-6.6 were slightly lower. The use of aryl iodides resulted in racemic product, due to a non-cationic aryl palladium-olefin intermediate; however, when silver salts were added, the enantioselectivity of the reaction did not improve.
Mechanistic investigations revealed the following: upon Heck reaction of phenyltriflate and 6.4 the cationic complexes (R)-6.9 and (S)-6.9 are formed after β'-hydrogen abstraction. Due to unfavourable steric interactions (S)-6.9 rapidly dissociates resulting in (S)-6.6. The olefin in (R)-6.9 however, is able to reinsert to provide (R)-6.10 and following a second hydrogen elimination and dissociation, results in (R)-6.5. The overall effect is a kinetic resolution of (R)-6.6 and (S)-6.6. Note that the initial ratio of (R)-6.7 and (S)-6.7 will not be 50:50 (so not a racemate) due to the use of (R)-BINAP that has a preference for the formation of (R)-6.7. This also implies that, if the reaction conditions are such that they promote formation of (S)-6.6 (so formation of the regioisomer (S)-6.5 does not take place), the e.e. of the major product (R)-6.5 will be higher. This has been shown by Hayashi.\textsuperscript{13}

\textbf{Scheme 6.3} \textit{Mechanism involved in the AHR of phenyltriflate to dihydrofuran.}

\textbf{Scheme 6.2} \textit{The intermolecular asymmetric Heck reaction of phenyltriflate with dihydrofurane.\textsuperscript{11}}
Reiser showed that, by increasing the pressure, the rate and turnover number could be increased in this reaction.\textsuperscript{14} Furthermore, several intermediates in this catalytic conversion have been identified and characterised.\textsuperscript{15}

### 6.2.2 Other ligands

Although the predominantly used ligand is still BINAP, several other ligands have been successfully employed in this asymmetric reaction. Amongst these are alkyl or alkoxy substituted BINAP analogues (diphenyl or dinaphthyl diphosphines),\textsuperscript{16} BINAs,\textsuperscript{17} and heterocyclic analogues of BINAP.\textsuperscript{18} The results obtained are very similar: conversions, rates, regioselectivities and enantioselectivities are comparable or slightly lower than BINAP. Bidentate P-N ligands, originally introduced by Pfaltz,\textsuperscript{19} representing another class of ligands, which have been successfully employed in the Heck coupling. Analogous ligands derived from proline or ketopinic acid were developed by Gilbertson.\textsuperscript{20} Hayashi reported a binaphthyl based phosphine-oxazoline,\textsuperscript{21} whereas Hou and Guiry described the use of ferrocenylphosphine oxazolines.\textsuperscript{22} A number of other analogues have been reported.\textsuperscript{23} These phosphine-oxazoline ligands are very efficient and can be used with a large range of alkenes, using a variety of aryl and vinyltriflates. The most interesting property of this catalyst system is, that the minor regioisomer 6.6 observed in the Pd-BINAP catalysed reaction is the only product in this case, with up to 99\% e.e. This means, that for this type of catalyst the kinetic resolution does not play a significant role. (see Scheme 6.4).

![Scheme 6.4](image)

\textbf{Scheme 6.4} \textit{Intermolecular AHR catalysed by Pd-phosphine-oxazoline complexes; no kinetic resolution is present which leads to the formation of only one regioisomer.}

The intermolecular asymmetric Heck reaction is not limited to 2,3-dihydrofuranes. The use of a number of other alkenes, including pyrans and other cyclic alkenes, has been reported.\textsuperscript{24}
6.3 Goal of this research

All ligands used so far for the asymmetric Heck reaction are bidentate and usually bisphosphines or phosphate-oxazoline ligands are employed. Despite the fact that the classic Heck reaction was shown to occur in the presence of phosphoramidites, the use of phosphoramidites as chiral ligands in an AHR resulted in very low enantioselectivity. This is particularly remarkable, because these ligands have proven to be very suitable for a number of asymmetric C-C bond formations. They are also surprisingly stable and very easy to prepare. Therefore, in the following sections, we will summarise the results of an investigation on the use of phosphoramidite ligands in the intermolecular AHR in order to elucidate whether they are a suitable addition to the number of ligands known to date and whether it was possible to use monodentate ligands for this reaction.

6.4 Results

6.4.1 Ligand screening

To achieve information about the applicability of phosphoramidites in the AHR, the standard intermolecular AHR of phenyl triflate to dihydrofuran was chosen as a test reaction. (See Scheme 6.5) Reactions were run for 21h or 67h at elevated temperatures under an inert atmosphere and an excess of dihydrofuran was used (6 equiv.), due to the volatility of this compound. The catalysts were prepared in situ from Pd(OAc)\(_2\) or Pd\(_2\)dba\(_3\) and ligands. The conversion was monitored by GC (dodecane was used as an internal standard).

Binaphthol based monodentate phosphoramidites L1 and L2, Taddol based phosphoramidites L4 and L5 and binaphthol based bidentate phosphoramidite L3 were applied as ligands. (see Figure 6.2) The catalyst was prepared in situ (6% Pd(OAc)\(_2\), 18% monodentate ligand, 12% bidentate ligand) in benzene or THF. Proton Sponge (PS, 1,8-bis(dimethylamino) naphthalene) was used as a base, and reactions were run at 40°C, for 67 h. We were very surprised to see that the only ligand that gave any conversion was L1, i.e. 29% conversion in benzene as the solvent. When Pd\(_2\)dba\(_3\) was used as a Pd-source, no conversion was observed in all cases. Increasing the L/Pd ratio (for L1) did not improve the conversion.
6.4.2 Solvent dependence
When several solvents were tested at different temperatures for the L1/Pd catalysed AHR reaction, we observed low conversions and very low ee’s for the products. (see Table 6.1) (ee’s 0-10%) The regioselectivity, however, showed an interesting temperature dependence. In all cases, when the reaction was performed at 40°C, the conversion was low, but the only product formed was the kinetic resolution product 6.5. Increasing the temperature to 70°C resulted in an opposite 6.5:6.6 ratio: an excess of 6.6 was formed in all cases. This implies that, at higher temperature, the kinetic resolution-pathway is less favourable and the temperature effects on the different pathways are different.

Table 6.1 AHR of 2,3-dihydrofuran (6 equiv.) and phenyl triflate

<table>
<thead>
<tr>
<th>Entry</th>
<th>Solvent</th>
<th>T (°C)</th>
<th>Conv (%)</th>
<th>Ratio 6.5:6.6</th>
<th>Ee (%) 6.5</th>
<th>Ee (%) 6.6</th>
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<tbody>
<tr>
<td>1</td>
<td>Benzene</td>
<td>40</td>
<td>14</td>
<td>1:0</td>
<td>1</td>
<td>3</td>
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<tr>
<td>2</td>
<td>Benzene</td>
<td>70</td>
<td>23</td>
<td>2:8</td>
<td>0</td>
<td>5</td>
</tr>
<tr>
<td>3</td>
<td>Toluene</td>
<td>40</td>
<td>5</td>
<td>1:0</td>
<td>11</td>
<td>-</td>
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<tr>
<td>4</td>
<td>Toluene</td>
<td>70</td>
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<td>4</td>
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<td>1:0</td>
<td>1</td>
<td>-</td>
</tr>
<tr>
<td>6</td>
<td>DMSO</td>
<td>70</td>
<td>30</td>
<td>1:9</td>
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</tr>
<tr>
<td>7</td>
<td>CH₃CN</td>
<td>40</td>
<td>11</td>
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<td>70</td>
<td>42</td>
<td>4:6</td>
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Reaction conditions: 20h, base: PS (3 equiv.), in situ prepared catalyst of Pd(OAc)₂/L1 (1/3, 6 mol%) conversion of PhOTf, determined by chiral GC, using dodecane as an internal standard. b relative ratio as determined by chiral GC. c determined by chiral GC.
6.4.3 Base dependence

It has been reported that the base used in the AHR can have a profound effect on both conversion and ee.\textsuperscript{1,11,20} Most frequently used bases include amines, but also carbonates and acetates have been employed. A number of bases were tested in the L1/Pd(OAc)\textsubscript{2} catalysed AHR of PhOTf to dihydrofuran 6.4 (see Table 6.2), and we indeed observed a strong base dependence in this reaction. In all cases, conversions were very low and the best results (14 % conv) were obtained using PS. For \textit{i}Pr\textsubscript{2}EtN, there was a strong preference for the formation of 6.6 (ratio 6.5:6.6 = 1:19). The influence on the ee was also interesting. Of the organic bases used, only Et\textsubscript{3}N was able to induce some enantioselectivity and although there was only 5% conversion, 6.6 was obtained with an ee of 24%. With inorganic bases Na\textsubscript{2}CO\textsubscript{3} and K\textsubscript{2}CO\textsubscript{3} only 5% conversion was seen, with a 1:1 ratio for both regioisomers. K\textsubscript{2}CO\textsubscript{3} provided the products as racemates, whereas Na\textsubscript{2}CO\textsubscript{3} gave the highest ee’s observed so far. Although 34% ee for 6.5 and 52% ee for 6.6 was obtained, these results were difficult to reproduce. On use of Cs\textsubscript{2}CO\textsubscript{3} no conversion was observed.

Table 6.2 AHR of dihydrofuran and phenyl triflate.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Base (3 equiv.)</th>
<th>Conv \textsuperscript{a} (%)</th>
<th>Ratio \textsuperscript{b} 6.5:6.6</th>
<th>Ee (%) \textsuperscript{c} 6.5</th>
<th>Ee (%) \textsuperscript{c} 6.6</th>
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<td>\textit{i}Pr\textsubscript{2}EtN</td>
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<td>1:19</td>
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<td>1:0</td>
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<td>3</td>
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<td>1:1</td>
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<tr>
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<td>NaOAc</td>
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</tbody>
</table>

Conditions: In situ prepared complex of Pd(OAc)\textsubscript{2}/\textit{L1} (1/3, 6 mol%), 20h/40°C, solvent: benzene, 6 equiv. of dihydrofuran 6.4. \textsuperscript{a} conversion of PhOTf, determined by chiral GC, using dodecane as an internal standard, \textsuperscript{b} relative ratio as observed by chiral GC, \textsuperscript{c} determined by chiral GC.

For a number of experiments, the reactions were repeated, only with iodobenzene as the phenyl-source in stead of PhOTf. No conversion was observed, not even when silver salts were added to obtain a cationic Pd-intermediate.
6.5 Conclusions

The results obtained using phosphoramidites as ligands for the intermolecular AHR were very disappointing as low conversions were obtained as well as low or poorly reproducible ee’s. In many cases Pd-black was formed during the reaction, indicating that a very unstable catalytic complex is present in solution. The major problem in applying phosphoramidites as ligands for these intermolecular AHR is that the reaction in our hands never went to full conversion. In general conversions of less then 20% were observed, even after prolonged reaction times. Although other phosphoramidites, which were not examined in the study described here, in the future might turn out to be efficient ligands for this reaction, the intramolecular AHR will probably give faster reaction times and will therefore be a more suitable test reaction to demonstrate that phosphoramidites are suitable ligands for the AHR. Therefore, in the next chapter, the results of the intramolecular AHR using Pd-phosphoramidite catalysts will be described.

6.6 Experimental procedures

For general remarks, see previous chapters. L1-L5 were prepared according to known literature procedures.28,30

Typical procedure for the intermolecular AHR of dihydrofuran and phenyl triflate:
In a flame dried flask, a mixture of Pd(OAc)$_2$ (6.6 µmol, 6 mol%), monodentate ligand (19.8 µmol, 18 mol %) was stirred in 1 ml of solvent for 10 min, until the colour became bright yellow. Internal standard (dodecane, 100 µL), base (0.66 mmol, 3 equiv.), 2,3-dihydrofuran (77.5 mg, 1.105 mmol, 5 equiv.) and phenyl triflate (50 mg, 0.221 mmol) were added and the mixture was stirred for the appropriate time at elevated temperatures. An aliquot of the reaction mixture was filtered through a small column of SiO$_2$ using heptane/IPA (90/10) as an eluent and the sample was analysed by chiral GC.

2-Phenyl-2,3-dihydrofuran (6.5)$^{31}$
$^1$H NMR $\delta$ 2.58 (ddt, $J = 15.4, 8.4, 2.6$ Hz, 1H), 3.05 (ddt, $J = 15.4, 8.4, 2.6$ Hz, 1H) 4.92 (q, $J = 3$ Hz, 1H), 5.49 (dd, $J = 11, 8$ Hz, 1H), 6.43 (q, $J = 3$ Hz, 1H), 7.20-7.40 (m, 5H). $^{13}$C NMR $\delta$ 38.1 (t), 82.5 (d), 99.2 (d), 125.8 (d), 127.8 (d), 128.7 (d), 143.3 (s), 145.5 (s). HRMS calc. for C$_{10}$H$_{10}$O$_2$ 146.073, found 146.072. GC-separations: Chiraldex G-TA (50mx0.25mm) $T_{\text{oven}}$ 70°C, $1^\circ$C/min $T_{\text{max}}$ = 150°C, rt 38.16 ($S$)-6.5, 38.98 ($R$)-6.5.

2-Phenyl-2,5-dihydrofuran (6.6)$^{23c}$
$^1$H NMR $\delta$ 4.86 (m, 2H), 5.76 (m, 1H), 5.89 (dq, $J = 5.9, 1.1$ Hz), 6.04 (dq, $J = 5.9, 1.6$ Hz, 1H), 7.32 (m, 5H). $^{13}$C NMR $\delta$ 76.2 (t), 88.3 (d), 126.3 (d), 126.5 (d),
127.7 (d), 128.4 (d), 129.9 (d), 142.0 (d). HRMS calc. for C_{10}H_{10}O 146.073, found 146.073.
GC-separations: Chiraldex G-TA (50mx0.25mm) T_{oven} 70°C, 1°C/min T_{max} = 150°C, rt 45.41 (S)-6.6, 46.43 (R)-6.6.

6.7 References

5 See chapter 7.
29 One additional equiv. of phosphoramidite is assumed to be needed to reduce the PdII to Pdio.