Hydrogenations and hydro-acylations using homogeneous platinum metal catalysts

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Chapter 3. Enantioselective Hydro-acylations of 1-Alkenes to $\alpha$-Methylketones using Palladium/Diphosphine Catalysts

3.1 Introduction

Asymmetric catalysis is an excellent methodology for the synthesis of chiral building blocks for the fine-chemical and pharmaceutical industry. A wide variety of chemical transformations can nowadays be carried out in a catalytic asymmetric fashion. Well known examples are the synthesis of (–)-menthol using chiral BINAP-rhodium catalysts and Naproxen, where a chiral phosphine is used in a hydrocyanation reaction (not commercialised). However, synthetic routes to enantiopure $\alpha$-alkyl-substituted ketones by catalytic asymmetric strategies are limited to date, despite the presence of especially the $\alpha$-methyl carbonyl moiety in a variety of natural products and biologically active compounds. To the best of our knowledge, the catalytic asymmetric synthesis of $\alpha$-methyl ketones has only been accomplished by means of baker’s yeast in the reduction of $\alpha$-methylene ketones.

A potentially very attractive catalytic methodology for the synthesis of $\alpha$-methylketones is the palladium catalysed hydro-acylation of 1-alkenes with syngas (Scheme 3.1).

$$\text{Scheme 3.1 Hydro-acylation of 1-alkenes to $\alpha$-substituted ketones.}$$

Besides the desired saturated ketones, however, a range of other products may be formed. Examples are enones (unsaturated ketones), oligo- and polyketones by co-polymerisation reactions and aldehydes/ alcohols by hydroformylation reactions (Scheme 3.2).
Scheme 3.2 Possible by-products for olefin hydro-acylations (for brevity, only one of the possible isomers is shown)

In addition, the hydro-acylation of olefins like 1-pentene can result in the formation of three saturated monoketone regio-isomers (Figure 3.1).

Drent and Budzelaar have demonstrated that the use of palladium catalysts of the type $(L_2)\text{PdX}_2$, where $L_2$ represents a bidentate alkylphosphine and $X$ stands for a weakly or non-coordinating anion$^{10,11}$, allows the selective production of monoketones. Very promising results were obtained using alkyl-diphosphines like 1,3-bis(di-n-butylphosphino)propane (DnBPP) in combination with Pd(OAc)$_2$ and trifluoromethanesulphonic acid (HOTf). For 1-octene, a monoketone chemoselectivity of 98 mol% was obtained with a head-to-tail regio-selectivity of 98 mol%.$^{10,11}$ The counter-ion plays a major role and when trifluoroacetic acid (TFA) instead of HOTf was used as the anion, the selective formation of aldehydes was observed.
An asymmetric version of the palladium catalysed hydro-acylation of 1-alkenes to monoketones has to the best of our knowledge not been reported to date. However, the use of chiral palladium catalysts \((L_2)\text{PdX}_2\) for the closely related asymmetric copolymerisation and oligomerisation of 1-alkenes with CO is known (Scheme 3.3).\(^{12-14}\)

\[
\text{CH}_2\text{Cl}_2, 20^\circ\text{C}, 96 \text{ h, 3 atm olefin, 20 atm CO}
\]

\[
\begin{array}{c}
\text{[Pd(L)(CH_3(CH_2CN))]BAr}_4 \\
(0.18 \text{ mol%})
\end{array}
\]

Scheme 3.3 Copolymerisation of CO/propene with a palladium-BINAPHOS catalyst system.

Consiglio reported the asymmetric alternating copolymerisation of propene and CO using the chiral Bichep ligand (Figure 3.2) with about 72% enantioselectivity.\(^{15-17}\) Further improvements were made by Sen who obtained enantioselectivity’s exceeding 90% when using Me-Duphos as ligand (Figure 3.2).\(^{16,17}\)

Figure 3.2 Chiral ligands for 1-alkene-CO co-polymerisation.

Other examples involve the use of BINAPHOS (Scheme 5)\(^{12-14,16}\) and ferrocenyl-type ligands (e.g. Josiphos ligands, Figure 3.2).\(^{16,18}\) For 1-propene-CO copolymerisations, high regioregularities (>99% head-to-tail) and high stereoregularity (> 96% isotacticity) were obtained. For high productivity and regioselectivity, the combination of a basic PCy\(_2\) and a more electron withdrawing PAr\(_2\) moiety appeared necessary. With the proof of concept for asymmetric induction available for the synthesis of medium-high molecular weight components, further activities shifted to the synthesis of chiral 1-alkene-CO dimers. For instance, Consiglio reported
the diastereo- and enantioselective synthesis of low molecular weight copolymers from propene and carbon monoxide in the presence of methanol to produce dimethyl-4-oxopentanoates.\textsuperscript{18,19} The use of modified Bichep ((R)-MeO-Bichep) and Josiphos ligands gave the highest regioselectivity for head-to-tail enchainment, although the diastereoselectivity (66\%) and enantioselectivity (72\%) were lower for the Josiphos ligand when compared to the selectivity’s obtained for copolymer synthesis.\textsuperscript{19,20}

The aim of the current study is the development of an asymmetric version of the hydroacylation of 1-pentene to give 4-methyl-5-decanone with high chemo-, regio- and enantioselectivity (Scheme 3.1). For this purpose, chiral Pd complexes of the type $L_2\text{PdOTf}_2$ were applied. Four different classes of chiral diphosphines ligands were tested (Josiphos, Duphos, Walphos and ferroTane) at a range of process conditions. The first two ligand classes were selected on the basis of successful asymmetric conversions of CO/1-alkenes to chiral oligomers and polymers (vide supra).

### 3.2 Experimental

#### 3.2.1 Chemicals

All chiral diphosphine ligands were obtained from Strem Chemicals. The ligands and the palladium acetate precursor (Sigma Aldrich >98\%) were stored in a glove box. Dichloromethane (Lab-Scan 99.8\%) and methanol (Lab-Scan 99.8\%) were distilled from CaH$_2$ before use and stored under nitrogen. 1-Pentene (Sigma Aldrich 98\%) was distilled from sodium and stored under nitrogen.\textsuperscript{21,22} Trifluoromethanesulfonic acid (HOTf) (Strem 99+\%) was stored under nitrogen at 5 °C. The synthesis gas used was a 50:50 pre-mixed CO/H$_2$ gas mixture (HiQ, high quality) and was purchased from Hoek Loos. Racemic 4-methyl-5-decanone was synthesised using established procedures.\textsuperscript{8,23} Enantio-enriched (80\% ee) 4-methyl-5-decanone was synthesised in a four step procedure.\textsuperscript{8,24} Enantio-enriched 4-methyl-nonanone (90\% ee) was prepared using a three step procedure.\textsuperscript{8,25} The tail-to-tail monoketone, 6-undecanone, was purchased from Sigma Aldrich (97\%).
3.2.2 Experimental set-up

The catalytic reactions were carried out in a Parr autoclave (50 ml), which was operated in a batch mode with respect to the gas phase (Figure 3.3). The maximum operating pressure of the reactor is 200 bar, the maximum temperature 200 °C. The reactor is electrically heated and the reactor content is stirred by a Parr overhead stirrer, equipped with a gas inducing impeller. Temperature and stirring speed are controlled by the Parr 4843 controller. The synthesis gas was fed from a premixed (50/50) storage bottle.

Figure 3.3 Schematic representation of the reactor setup.

3.2.3 General procedure

The catalyst was freshly prepared before each experiment under a protective nitrogen atmosphere using standard Schlenk techniques. Pd(OAc)$_2$ (9 mg, 0.04 mmol) was dissolved in the reaction solvent (either dichloromethane or methanol, 2 mL). After approximately 10 min the
diphosphine ligand (0.04 mmol) dissolved in either dichloromethane or methanol (2 mL) was added. The solution was stirred for 10 min prior to the addition of HOTf (30 mg, 0.2 mmol) and stirred for another 10 minutes before use. The batch autoclave was charged with solvent (either dichloromethane or methanol, 10 ml), 1-pentene (4.0 ml, 36.5 mmol) and the catalyst solution. The reactor was closed and flushed with nitrogen to remove air. The reactor was pressurised (60 bar) with synthesis gas (50/50 H\textsubscript{2}/CO) and stirring was applied (1000 rpm). Subsequently the reactor was heated to the desired reaction temperature (60 or 125 °C). After 5 h, the reactor was cooled to room temperature, depressurised, and flushed several times with N\textsubscript{2}. The liquid product was filtered over silica gel to remove the catalyst.

### 3.2.4 Product analyses

The product composition in the liquid phase was analysed using a GC-FID HP-5890 series II, equipped with a 30 m HP-1 column and He as the carrier gas. The following temperature profile was applied: 10 minutes at 30 °C, from 30 °C to 325 °C at a rate of 10 °C/min, 15 min at 325 °C. Product compositions were obtained by comparing product peak areas by means of the 100% method.\(^{26}\) The method was applied for peaks belonging to the most abundant product groups present in the samples: mono-oxygenates (ketones, aldehydes/alcohols and esters), olefin dimers and diketones. The response factors of all individual components are not known. To compensate for this, the concept of effective carbons was applied to determine the mol fraction of a product as is given in equation 3.1.\(^{27}\)

\[
X_j = \frac{F_j(\sum C_{ef})_j}{\sum_i \frac{F_i}{(\sum C_{ef})_i}} \quad (3.1)
\]

Here \(X_j\) stands for the mol fraction of component \(j\) and \(F_j\) stands for the peak area of component \(j\). \(F_j\) is divided by the sum of its effective carbons \((C_{ef})\) to obtain the ‘effective area’ of component \(j\). The effective area of component \(j\) is divided by the sum of all effective areas of the relevant components in the chromatogram.\(^ {28}\)

The 1-pentene conversion was determined by GC. The concentration of 1-pentene in the liquid phase after reaction was determined using calibration curves with known 1-pentene
concentrations. The product solution was directly analyzed after reaction to avoid excessive evaporation of 1-pentene.

Product identification was performed by GC-MS and GC. GC-MS chromatograms were recorded on a GC (HP 6890) MS (HP-5973) equipped with a 30 m HP-5 MS column and He as the carrier gas (from 35 °C to 250 °C, rate 5 °C/min, final time 10 min.). GC spectra were recorded on a GC-FID HP-5890 series II, FID with a 30 m HP-1 column and He as the carrier gas (vide supra). Reference compounds, either obtained from chemical suppliers or prepared, were used to identify relevant components in the mixture.

The enantiomeric excess (ee) of 4-methyl-5-decanone was determined using a GC equipped with a 30 m chiral β-PM column with He as the carrier gas. The following temperature profile was applied: Initial temperature at 55 °C, hold time 100 min, then from 55 °C to 180 °C, rate 10 °C/min, final time 15 min. The retention times of the enantiomers were at 107.9 and 108.3 minutes at these conditions. A solvent change was required before the reaction products could be injected. For this purpose, the reaction solvent was removed under reduced pressure (100 mbar, 30 °C) to give yellow oil. The oil was re-dissolved in diethyl ether and analysed. The chromatograms were compared with the GC-MS and GC-FID analyses for peak identification and to identify possible overlap of individual enantiomers with by-products. Also the chromatograms were compared with those obtained with the reference materials (see section 3.2.1).

3.3 Results

The catalyst precursors \((L_2)\text{Pd(OTf)}_2\) were made in situ by mixing \(\text{Pd(OAc)}_2\), the corresponding diphosphine and trifluoromethanesulfonic acid (HOTf) in either dichloromethane or methanol, see Scheme 3.4.\(^{10,11}\)

\[
L_2 + \text{Pd(OAc)}_2 + 2\text{HOTf} \rightarrow (L_2)\text{Pd(OTf)}_2 + 2\text{HOAc}
\]

Scheme 3.4 In situ formation of the catalyst precursor.
For all experiments a Pd to L$_2$ to HOTf molar ratio of 1.0 to 1.0 to 5.0 was applied. Experiments with different chiral diaphosphine ligands belonging to four ligand families (Josiphos, Duphos, Walphos and ferroTANE) were performed.

### 3.3.1 Initial screening experiments using the a typical Josiphos ligand

Initially, a typical (R,S)-Josiphos ligand (L$_1$, Figure 3.4) was screened in dichloromethane at 125 ºC and 60 bar pressure with a 1-pentene to catalyst ratio of 913 mol/mol. The results are given in Table 3.1 (entry 1).

![Figure 3.4 Josiphos ligand L$_1$](image)

**Table 3.1 Hydro-acylation of 1-pentene with Pd/(R,S)-Josiphos catalysts L$_1^a$**

<table>
<thead>
<tr>
<th>Entry</th>
<th>T (°C)</th>
<th>Solvent</th>
<th>Sat. MK (%)</th>
<th>Sat. MK$_{h-to-t}$ (%)</th>
<th>Sat. MK$_{t-to-t}$ (%)</th>
<th>h-to-t (%)</th>
<th>t-to-t (%)</th>
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<th>S$_{MK}$ (±)</th>
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<th>Aldehydes/Alcohols (%)</th>
<th>Esters (%)</th>
<th>Diketones (%)</th>
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</table>

a. Intake: 36.5 mmol of 1-pentene; 0.04 mmol of Pd; 0.04 mmol L$_2$; 0.2 mmol HOTf as the acid, 5 h reaction time, P$_{H_2}$ = P$_{CO}$ = 30 bar. b. Products: Sat. MK: saturated monoketones (all regio-isomers); Enones: unsaturated monoketones (all regio-isomers); Total product composition = 100%. c. Fraction of saturated h-to-t monoketone or saturated head-to-head monoketone in the saturated MK fraction (h-to-h regio isomers were below the GC detection limit). d. Definition given in eq. 2. e. ee of the saturated head-to-tail monoketone, 4-methyl-5-decanone.
The enantiomeric excess (ee) of the desired 4-methyl-5-decanone, the head-to-tail monoketone, was negligible under these conditions. The selectivity towards 4-methyl-5-decanone (S_md) was 78 mol%. Here the selectivity is defined as in equation 3.2.

\[
S_{md} = (\text{saturated mono-ketones}) \times (h-t \text{ fraction in saturated mono-ketones}) \text{ (mol\%)} \tag{3.2}
\]

Besides the desired saturated monoketones, small amounts of enones, diketones and olefin dimers (GC-MS, M^+ = 140) were formed as well. The formation of diketones and enones is in line with literature data for achiral hydroacylations using L_2Pd(OTf)_2 catalysts with alkyldiphenosphines.\(^{10,11}\)

The olefin dimer fraction consisted of a mixture of isomeric C10 mono-unsaturated olefins of which the position of the double bond and the level of branching could not be established. The palladium catalysed dimerisation of olefins using diphosphine-palladium complexes of the type (P_2)PdX_2 is well known in the literature. Examples are the dimerisation of ethylene using Ph_2P-(CH_2)_3-PPh_2 in combination with Pd(OAc)_2 and p-toluene sulphonlic acid (95 °C, 40 bar ethylene pressure) to give C4 dimers in more than 98% yield\(^{29,31}\), the use of similar cationic Pd compounds with BF_4^- anions for the dimerisation of ethylene, propylene and styrene\(^{32}\) and asymmetric styrene dimerisation using mixed palladium-indium species containing phosphite ligands.\(^{33}\) However, olefin dimerisation under syngas conditions is remarkable. A further discussion and mechanistic implications will be given in the final section of this paper.

The selectivity for the desired 4-methyl-5-decanone is not only a function of the chemoselectivity but also a good regioselectivity towards the head-to-tail isomer is required. The regioselectivity in dichloromethane is excellent and the desired head- to-tail isomer was formed predominantly (97%), the remainder being mainly the tail-to-tail regio-isomer.

Various 1-pentene isomers were also found in the reaction mixture, a clear indication that the catalyst is also active in olefin isomerisation. This is not surprising as cationic Pd complexes of the type (P_2)Pd^+ X^- are well established olefin isomerisation catalysts.\(^{34-38}\)

To improve enantioselectivity, a hydro-acylation reaction was carried out at 60 °C instead of 125 °C. At these conditions, indeed a small though measurable ee was observed (4%, see Table 3.1, entry 2). However, the selectivity towards 4-methyl-5-decanone was reduced from 78 to 39 mol% due to the formation of considerable amounts of enones (36 mol%) and diketones (19
Chapter 3

The formation of higher levels of diketones indicates that subsequent CO and olefin insertions occur more easily at lower temperatures leading to higher molecular weight products. This is a well established feature for CO/olefin co-oligomerisations and copolymerisations. The formation of higher amounts of enones at 60 °C implies a change in termination mechanism when lowering the temperature. Both the saturated monoketones and enones are formed from a common intermediate (vide infra). Termination by β-hydrogen elimination leads to enones, reaction with hydrogen to saturated monoketones. The shift towards enone formation suggests that termination by β-hydrogen elimination instead of the reaction with hydrogen becomes more pronounced at lower temperatures. A similar trend was reported by Drent and Budzelaar for related achiral Pd/diphosphine systems. Thus, lowering the temperature seems favourable for the enantioselectivity but has a negative effect on the chemoselectivity to saturated monoketones.

The 1-pentene conversion after 5 h at 60 °C was 84%. This corresponds with an average turnover frequency (TOF) of 150 mol/(mol Pd.h). Typical values reported in the literature for achiral hydroacylations using alkylphosphines at 115 °C are about 1000 mol/(mol Pd.h) for 1-propene and about 100 mol/(mol Pd.h) for higher olefins like 1-octene. Thus, particularly when considering the relatively low temperature for the experiment with the Josiphos ligand, the TOF for the Josiphos ligand is at the high end of the range given in the literature.

When the reaction was carried out in methanol (Table 3.1, entry 3), the selectivity to 4-methyl-5-decanone was only 16 mol%. Surprisingly, the major products here were alcohols/alddehydes (42 mol%) and esters (40 mol%). The alcohols/alddehydes are formed by hydroformylation (Scheme 3.2), the esters by methoxycarbonylation (Scheme 3.5), which are well established reaction pathways for syngas-1-alkene conversions in methanol using (L₂)PdX₂ catalysts, although no specific examples are known for the catalyst used here (with ferrocenyl type of ligands and HOTf). Thus, methanol is not inert and is incorporated partly in the product.

\[
\text{Scheme 3.5 Methoxycarbonylation of 1-pentene.}
\]
From these preliminary experiments it is concluded that Josiphos ligands are potentially attractive for hydro-acylation reactions, though the enantioselectivity for L1 is poor at the conditions employed. The chemoselectivity of Josiphos L1 in dichloromethane (high ketone selectivity, some diketones) shows resemblances with the results for typical cationic palladium-containing alkyldiphosphines like DnBPP and 1,3-bis(di-s-butylphosphino)propane (DsBPP) with HOTf as anion source.\textsuperscript{10,11} However, the chemoselectivity in methanol differs considerably. With typical alkyldiphosphines like DsBPP and strong acids as the anion source, ketones are by far the main product and esters are not produced in considerable amounts when the reactions are performed in methanol. Only using the sterically very congested alkyldiphosphines like 1,3-bis(di-t-butylphosphino)propane, methyl esters are the main product.\textsuperscript{41} Thus, the Josiphos ligand L1 cannot be classified simply as an alkyldiphosphine and shows dual properties, in line with the presence of both an alkyl and arylphosphine group in the structure (Figure 3.4).

Based on the experiments with Josiphos L1, it was concluded that the subsequent screening experiments with a broader range of chiral ligands could be best performed in dichloromethane instead of methanol. A temperature of 60 °C or below was anticipated to have a positive effect on the enantioselectivity, although this might be at the expense of the chemoselectivity as well as the rate of the reaction.

### 3.3.2 Screening experiments with the Josiphos ligand family

The Josiphos ligands for the screening experiments are given in Figure 3.5. The experiments were performed at a reaction temperature of 60 °C in dichloromethane with 1-pentene as the olefin and using 30 bar H\textsubscript{2} and 30 bar CO pressure.
Figure 3.5 Josiphos type ligands L2-10

An overview of the results for the hydro-acylation reactions using the chiral Josiphos ligands is given in Table 3.2.
Enantioselective hydro-acylations of 1-alkenes to α-methylketones

Table 3.2 Overview of results for catalytic hydro-acylations using the chiral Josiphos ligand family.a.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Ligand</th>
<th>Sat. MK (%)</th>
<th>Sat. MK h-to-t (%)</th>
<th>Sat. MK t-to-t (%)</th>
<th>ee (%)</th>
<th>Enones (%)</th>
<th>Aldehydes/Alcohols (%)</th>
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a. Intake: 36.5 mmol of 1-pentene; 0.04 mmol of Pd; 0.04 mmol L₂; 0.2 mmol HOTf as the acid, 5 h reaction time, P₁₂ = P₁₃ = 30 bar, dichloromethane, T = 60 °C. b. Products: Sat. MK: saturated monoketones (all regio-isomers); Enones: unsaturated monoketones (all regio-isomers); Total product composition = 100%. c. Fraction of saturated h-to-t monoketone or saturated head-to-head monoketone in the saturated MK fraction (h-to-h regio isomers were below the GC detection limit). d. Definition given in eq. 2. e. ee of the saturated head-to-tail monoketone, 4-methyl-5-decanone. f. Actual value likely lower due to some peak overlap in GC measurements. g. 15 mol% of 1-pentene dimers formed.

The enantioselectivity of the reaction is a clear function of the ligand. The highest ee for 4-methyl-5-decanone was 39% for ligand L₈. For ligand L₃, an ee of 25% was observed. However, the latter value is overestimated due to peak overlap of one of the enantiomers in the chiral GC chromatograms with small unidentified peaks. This was confirmed by comparing the chiral GC chromatograms with those obtained using a non-chiral GC column. The latter shows some, yet unidentified, additional peaks in the relevant region which hamper an accurate determination of the ee.

For all other ligands, the ee was below 5%. With this limited dataset, it is not possible to draw solid conclusions on the effects of the substituents of the Josiphos ligands (R and R’) on the enantioselectivity. To confirm the ee values for the best Josiphos ligand in the series, an experiment with the (S,R) enantiomer of ligand L₈ was performed. This gave the opposite
enantiomer of 4-methyl-5-decanone with an ee of 42% and confirms that chiral induction indeed occurred with this ligand.

Although L8 gave the highest ee of all Josiphos ligands, the selectivity to the desired 4-methyl-5-decanone (6 mol%) is at the low end of the range (4-48 mol%). This is visualised in Figure 3.6, where the selectivity is given as a function of the R and R’ substituents on the Josiphos ligand. The aromatic R substituents are ordered according to their electronic properties\textsuperscript{18,42,43}, although some electronic effects cannot be excluded \textit{a priori}. The R’ groups are divided into alkyl and aryl substituents. Apparently, the selectivity is highest when using an unsubstituted Ph group at position R, whereas the R’ group has a limited effect.

Figure 3.6 Selectivity to the 4-methyl-5-decanone (SMD) as a function of the P-substituents of the Josiphos ligands L1-10.
The selectivity for 4-methyl-5-decanone is a function of both the chemo- and regioselectivity of the hydro-acylation reaction. These effects will be discussed separately. For all Josiphos ligands, the chemoselectivity as a function of the substituents on the phosphine ligands is given in Figure 3.7.

![Figure 3.7 Chemoselectivity for the reaction of 1-pentene with synthesis gas using the Josiphos ligands L1-10. First number: saturated monoketone content (mol%); second: enone content, third: diketone content (mol%).](image)

The chemoselectivity towards saturated monoketone formation varies between 55 and 4 mol%. Other products were enones and diketones and in one case olefin dimers were formed as well (L7, 15 mol%). Particularly the enones were formed in large amounts (up to 77 mol%) and for some of the ligands enones are actually the main product. Alcohols and aldehydes were present in amounts less than 5 mol%. The highest chemoselectivity with respect to saturated monoketone formation was obtained with ligand L4 (entry 4, Table 3.1), namely 55 mol%. When considering Figure 3.7, the highest chemoselectivity to saturated monoketones was found for R
groups with intermediate electronic properties (Ph, 3,5-dimethyl-4-OMe-Ph) whereas the influence of the group \( R' \) seems limited.

For most of the ligands, the major regio-isomer in the saturated monoketone fraction is the desired head-to-tail regio-isomer (Figure 3.1). The only exceptions are ligand L\(_4\), L\(_8\) and L\(_{10}\) where the tail-to-tail isomers are predominantly formed. These three ligands contain an aromatic xyllyl group at the \( R' \) position and a phenyl or furan group at position \( R \) and may be viewed as aromatic diphosphines. It is well established in the literature that the use of arylphosphines leads to lower amounts of the head-to-tail regio-isomers than alkylphosphines.\(^{10,11}\)

Thus, it is concluded that chiral induction to obtain enantio-enriched 4-methyl-5-decanone is possible with Josiphos ligands. The best results were obtained with the (R,S)-L\(_8\) ligand and an ee of 39% was observed. Unfortunately, the selectivity of 4-methyl-5-decanone was low (6 mol%) with this particular ligand at the process conditions applied to obtain the 39% ee. The main issue is a poor regioselectivity leading to the formation of considerable amounts of the tail-to-tail regio-isomer.

### 3.3.3 Screening results for the Duphos ligand family and a Walphos and ferroTANE ligand

A number of experiments were performed with three members of the Duphos ligand family (Figure 3.8) and a Walphos and FerroTANE ligand (Figure 3.9). The experiments were carried out with 1-pentene at 60 °C in dichloromethane using 30 bar \( H_2 \) and 30 bar CO pressure.

![Figure 3.8 Duphos ligands.](image)

L\(_{11}\). (R,R)-Me-Duphos  L\(_{12}\). (R,R)-Et-Duphos  L\(_{13}\). (R,R)-i-Pr-Duphos

Figure 3.8 Duphos ligands.
Enantioselective hydro-acylations of 1-alkenes to α-methylketones

Figure 3.9 FerroTANE and Walphos ligand.

The results for all experiments are given in Table 3.3

Table 3.3 Overview of results for catalytic hydro-acylations of 1-pentene using the chiral Duphos, FerroTANE and Walphos ligands a.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Ligand</th>
<th>Sat. MK (%)</th>
<th>Sat. MK h-to-t (%)</th>
<th>SMD (%)</th>
<th>ee (%)</th>
<th>Sat. MK t-to-t (%)</th>
<th>Enones (%)</th>
<th>Aldehydes/Alcohols (%)</th>
<th>Diketones (%)</th>
<th>Olefin Conv. (%)</th>
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<tbody>
<tr>
<td>1</td>
<td>L11</td>
<td>69</td>
<td>95</td>
<td>66</td>
<td>16</td>
<td>5</td>
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<td>17</td>
<td>58</td>
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<tr>
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<td>L12</td>
<td>59</td>
<td>96</td>
<td>57</td>
<td>20</td>
<td>4</td>
<td>2</td>
<td>0</td>
<td>34</td>
<td>32</td>
</tr>
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<td>37</td>
<td>72</td>
</tr>
<tr>
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<td>16</td>
<td>44</td>
<td>7</td>
<td>4</td>
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<td>48</td>
<td>1</td>
<td>27</td>
<td>39</td>
</tr>
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<td>7</td>
<td>6</td>
<td>53</td>
<td>36</td>
<td>0</td>
<td>24</td>
<td>73</td>
</tr>
</tbody>
</table>

a. Intake: 36.5 mmol of 1-pentene; 0.04 mmol of Pd; 0.04 mmol L₂; HOTf as the acid; 5 h reaction time; P_H₂ = P_CO = 30 bar, dichloromethane, 60°C. b. Products: Sat. MK: saturated monoketones (all regio-isomers); Enones: unsaturated monoketones (all regio-isomers); Total product composition = 100%. c. Fraction of saturated h-to-t monoketone or saturated head-to-head monoketone in the saturated MK fraction (h-to-h regio isomers were below the GC detection limit). d. Definition given in eq. 2. e. ee of the saturated head-to-tail monoketone, 4-methyl-5-decanone. f. Actual value likely lower due to some peak overlap in GC measurements. g. 15 mol% of 1-pentene dimers formed.

The selectivity to the desired saturated head-to-tail monoketone (4-methyl-5-decanone) for the Duphos ligands (42-66 mol%) is considerably higher than for the best Josiphos ligand (<48 mol%). However, the ee of the product is between 6 and 20%, which is considerably lower than
the highest value observed for the L8 Josiphos ligand (39%) at similar conditions. The ee values are also likely slightly overestimated due to peak overlap in the chiral GC, as also observed for one of the Josiphos ligands (vide supra).

The chemoselectivity for saturated monoketone formation as a function of the substituents on the Duphos ligands is given in Figure 3.10. The values range between 42 and 69% and are considerably higher than for the Josiphos family (4-48 mol%). Major by-products are enones and diketones. Alcohols/aldehydes and olefin dimers were absent. The (R,R)-Me-Duphos (L11) ligand is the most selective for saturated monoketone formation. When increasing the bulk of the alkyl-substituent the preference for monoketone formation is reduced and diketones and enones are formed in considerable amounts.

![Figure 3.10 Chemoselectivity for the Duphos ligand family.](image)

Of particular interest is the high regioselectivity towards the desired saturated head-to-tail isomer for the Duphos ligand family (> 95 mol%). This observation is in line with earlier work by Drent et al. on the palladium catalysed hydrocarbonylation of propene. Of all diphosphine $R_2P(CH_2)_nPR_2$ ligands tested, alkyldiphosphine ligands led to higher amounts of the desired head-to-tail regio-isomer than arylphosphines.$^{10,11}$
The results for the Walphos and FerroTANE ligands (Figure 3.9) were not very promising. Low chiral inductions (ee < 6%) were observed (Table 3.3) and the selectivity to the desired saturated head-to-tail monoketone, 4-methyl-5-decanone, was also low (7 mol%). The poor selectivity is caused by a low chemoselectivity to saturated monoketones (large amounts of enones formed) and an intermediate regioselectivity (Table 3.3).

3.4 Discussion and mechanistic aspects

The hydrocarbonylation of olefins using (L₂)PdX₂ catalysts may lead to the formation of the desired monoketones (hydro-acylation) as well as to alcohols/aldehydes by hydroformylation and higher ketones by copolymerization reactions.¹⁰⁻¹¹ A proposed catalytic cycle including the formation of the various product classes is given in Scheme 3.6. The active species is commonly accepted to be a square-planar cationic Pd-hydride complex. Insertion of an olefin into the Pd-hydride bond followed by coordination and migratory insertion of a CO molecule results in the formation of a Pd-acyl species. The latter can either react with hydrogen (hydrogenolysis) to give an aldehyde/alcohol (hydroformylation) or with a second olefin leading to the formation of a Pd-alkyl species. Further successive insertions of CO and olefins will result in the production of polyketones (copolymerisation). Direct hydrogenolysis of the Pd-alkyl species will lead to the formation of saturated monoketones (hydro-acylation), whereas β-hydride elimination gives unsaturated monoketones (also hydro-acylation).
Scheme 3.6 Proposed catalytic cycle for the Pd(II) catalysed reactions of 1-alkenes and syngas.

3.4.1 Chemoselectivity

The chemoselectivity of the 1-alkene/syngas reactions catalysed by (L)$_2$PdX$_2$ complexes can be tuned by the choice of the diphosphine ligand, anion, reaction conditions and the solvent.\textsuperscript{10,11} When using the Josiphos ligand family for the palladium catalyst hydro-acylation of 1-pentene in DCM at 60 °C using the triflate anion, the chemoselectivity towards the desired saturated monoketones is between 4 and 55 mol%. The highest chemoselectivity is observed with the ligands containing a Ph group at position R. Enones (23-71 mol%) and diketones (4-36 mol%) are by far the most important by-products (Figure 3.7). Both the saturated monoketones and the enones are formed from the same intermediate, a Pd-alkyl species with a pendant ketone group...
Enantioselective hydro-acylations of 1-alkenes to α-methylketones

(Scheme 3.6). Enones are formed by β-hydrogen elimination, saturated ketones by hydrogenolysis. The formation of large amounts of enones is indicative for a strong electrophilic metal centre with a high affinity for β-hydrogen elimination. The relative reaction rates of both reactions determine the chemoselectivity of the reaction. Hydrogenolysis is assumed to proceed via heterolytic hydrogen splitting, where formally a H⁺ is transferred to the anion and H to the Pd centre. It is well possible that heterolytic splitting of hydrogen is rather difficult in this system due to the use of the triflate anion (a poor H⁺ acceptor) in combination with a relatively polar solvent, leading to a large Pd-anion distance.

Higher temperatures favour hydrogenolysis over β-hydrogen elimination, as is concluded from the observed temperature effects for L1 (higher amounts of saturated ketones at higher temperature, see Table 3.1). Another possible measure to reduce enone formation is to perform the reactions at higher hydrogen pressure to speed up the rate of the hydrogenolysis reaction.

The amount of saturated monoketones observed for the Duphos ligands (42-69 mol%) is much higher than for the Josiphos ligands. Apparently, termination by reaction with hydrogen is strongly favoured over β-hydride elimination for the Duphos ligands. Major by-products are diketones (17-37 mol%) and to a lower extent enones (4-16 mol%, Figure 3.10). The chemoselectivity is highest for the smaller Duphos substituent (Me) and particularly the diketone fraction increases when going from R = Me to R = 3Pr. This is a clear indication for a higher preference for CO insertion in the Pd-alkyl species with the pendant carbonyl group than hydrogenation/β-hydrogen elimination when using bulkier substituents.

Hydro-acylations with two of the Josiphos ligands and the Walphos ligand resulted in the formation of significant amounts of C10 mono-unsaturated olefins arising from 1-pentene dimerisation. The maximum amount was found for the Walphos ligand L15 (19 mol%, Table 3.3). Palladium diphosphine compounds are well known olefin dimerisation catalysts. However, dimerisations in the presence of CO have to the best of our knowledge not been reported to date. One possible explanation for olefin dimer formation is the (strong) acid catalysed (here HOTf) dimerisation of 1-pentene. However when valid, olefin dimerisation would be expected to occur for all reactions and this is certainly not the case. An alternative explanation is the involvement of cationic Pd catalysts, even though CO is present. In this case, olefin insertion has to compete with CO insertion in a Pd-alkyl bond. Support for the involvement of Pd complexes in the dimerisation reaction comes from a subsequent optimisation study using the Josiphos ligand L8.
Here, the content of olefin dimers in the reaction mixture was found to be a clear function of the CO pressure, with low pressures leading to a higher dimer contents. Thus, it is reasonable to assume that olefin dimerisation is a metal catalysed reaction and that the Josiphos ligand in this respect shows unique behaviour.

3.4.2 Regioselectivity

The regioselectivity of the saturated monoketone fraction depends on the mode of olefin insertion in a Pd-H bond (first insertion) and a Pd-acyl bond (second insertion, see Scheme 3.7). The desired head-to-tail isomer may be obtained by either two consecutive 1,2 insertions or two consecutive 2,1 insertions.

Scheme 3.7 Regioselectivity for saturated monoketone formation. 1,2; 1,2-insertion, 2,1: 2,1-insertion.
For the Josiphos ligand family, the regioselectivity towards the various saturated monoketone isomers (Figure 3.1) is a strong function of the R’ group (Figure 3.7), with alkyl substituents (tBu, Cy) leading to the highest amounts of the desired head-to-tail isomer. The head-to-head regioisomer was below the GC detection limit. This implies that 2,1 insertion of 1-pentene followed by 1,2 insertion does not occur to a significant extent. This is in line with literature data on related catalysts which indicate that 2,1 insertion of an-alkyl substituted olefin into a Pd-H bond does not take place easily.\textsuperscript{10,44} It suggests that the left pathway in Scheme 3.7 is the most likely. Thus, the desired 4-methyl-5-decanone is most probably formed by two consecutive 1,2 insertions of 1-pentene.

For the Josiphos ligands with xylyl substituents at the R’ position, the tail-to-tail isomers are predominantly formed. This suggests that the regioselectivity is a strong function of the basicity of the phosphine ligands, with less basic arylphosphines leading to a higher portion of the tail-to-tail isomer. This is in line with research by Drent et al. on the palladium(II) catalysed hydrocarbonylation of propene. Here the use of alkylphosphines led to higher amounts of the desired head-to-tail regioisomer than with the arylphosphines.\textsuperscript{10,11}

### 3.4.3 Enantioselectivity

The enantioselectivity’s for the desired saturated head-to-tail isomer, 4-methyl-5-decanone, is in general low and only for four ligands out of the sixteen tested, ee values exceeding 10% were observed. A possible reason for these relatively low ee values is enolization of already formed 4-methyl-5-decanone in the course of the reaction.\textsuperscript{45} We investigated this possibility by performing a hydro-acylation reaction in the presence of enantio-enriched 4-methyl-5-nanonone using a catalyst with $L_1$ as the diphosphine ligand for the hydro-acylation of 1-pentene (dichloromethane, 50 °C, 24 h, 60 bar, 1 to 1 CO/H\textsubscript{2} ratio). After the reaction, the ee of the added enantio-enriched 4-methyl-5-nanonone was similar to the starting material. This experiment indicates that in-situ racemisation during the reaction, at least at 50°C, is not likely.

The enantioselectivity of the reaction is most likely determined by the second insertion of the olefin in the Pd-alkyl bond (Scheme 3.6) and not by the first one. The second olefin insertion should proceed in a 1,2 fashion \textit{(vide supra)} to obtain the desired head-to-tail isomer (Scheme 3.7).
A possible explanation for the relatively low ee values is epimerisation of the stereogenic centre formed after the second olefin insertion. Epimerisation might occur by β-hydrogen elimination followed by re-insertion (Scheme 3.8). In this sequence the chirality at the α-position of the ketone is reduced or even lost.

The Pd-H species with the coordinated enone may rearrange to form a Pd-enolate, as was shown by Klusener et al. Two termination reactions may be envisaged: i. reaction of the chelate formed after the second olefin insertion step with hydrogen giving a Pd-H and 4-methyl-5-decanone and ii. reaction of the Pd-enolate with HOTf to form (racemic) 4-methyl-5-decanone and L₂Pd(OTf)₂. Thus, in case epimerisation plays a role and leads to a reduction of the product ee, the rate of epimerisation (initiated by β-hydrogen elimination) versus the rate of reaction of the Pd-alkyl bond with hydrogen will affect the product ee. When this hypothesis is valid and when assuming that the rate of hydrogenolysis is a function of the hydrogen pressure, higher product ee’s are expected at higher hydrogen pressures. All experiments performed so far were performed at a constant hydrogen pressure, making it impossible to ground this hypothesis.

The highest ee value in the Josiphos family was obtained for ligand L₈, an arylyphosphine with xylyl and 3,5-(CF₃)₂-Ph substituents. The question arises why this particular ligand gives the highest enantioselectivity. The chemoselectivity to saturated monoketones is within the range of the Josiphos ligands. More remarkable is a poor regioselectivity, actually by far the worst of all Josiphos ligands, with the dominant formation of the tail-to-tail isomer (87 mol% of the saturated monoketone fraction). It implies that 2,1 insertion for the second olefin insertion step is highly favoured. This change in insertion mode compared to the other ligands may either be steric or
electronic in origin. The common insertion mode for alkyl substituted terminal olefins is a 1,2 mode. Thus, one could argue that this change in regioselectivity has a steric origin, suggesting the presence of a rather crowded metal centre. This crowdedness might lead to a high enantio-discrimination for the insertion step. However, further studies (to be reported) for the L8 ligand at a wide range of process conditions reveal that modest ee values are also possible at good regioselectivities, indicating that this hypothesis is likely not valid. An alternative explanation for the performance of L8 could be a high rate of hydrogenolysis compared to epimerisation (Scheme 3.8). Support for this statement comes from the observation that the amount of enones is the lowest for all Josiphos ligands. Thus, β-elimination seems less facile than hydrogenation. When considering that epimerisation involves β-hydrogen elimination, although without release of the product olefin from the metal coordination sphere, it could be speculated that the rate of epimerisation compared to hydrogenolysis is low for L8, leading to enhanced product ee’s.

3.5 Conclusions

Sixteen chiral diphosphine ligands were screened for the chiral hydro-acylation of 1-pentene to 4-methyl-5-decanone (saturated head-to-tail monoketone) using Pd catalysts of the type (L2)Pd(OTf)2. The highest ee was found for the (R,S) Josiphos ligand L8 (39% ee), albeit the product selectivity was low (6 mol%) due to a poor regioselectivity. Enantiomeric discrimination by this ligand was confirmed by reactions with the (S,R) Josiphos ligand L8, giving the other enantiomer of 4-methyl-5-decanone with a similar ee. The highest ee value for a Duphos ligand was 20%, although this value is slightly overestimated due to peak overlap in chiral GC analyses. The selectivity to 4-methyl-5-decanone is much better for the Duphos ligands (up to 66 mol%) than the Josiphos ligands. The research described in this paper indicates that chiral induction in catalytic hydro-acylation reactions is possible and that both arylphosphines (Josiphos L8) and alkylphosphines (Duphos) have potential for further research to increase the ee and the yield. These studies will be reported in forthcoming papers.
3.6 References


Enantioselective hydro-acylations of 1-alkenes to α-methylketones


