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Optimization Studies on the Hydro-acylation of 1-Alkenes to α-Methylketones using a Homogeneous Palladium/Josiphos Catalyst

Hans Heeres,[†] Adri J. Minnaard,[‡] Bart Hessen,[‡] and Hero J. Heeres*,[†]

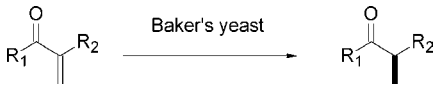
[†]Department of Chemical Engineering, ITM and [‡]Stratingh Institute for Chemistry University of Groningen, Nijenborgh 4, 9747 AG Groningen, The Netherlands

ABSTRACT: The effect of process conditions (temperature, partial pressures of CO and H_2) on the product selectivity and ee of the palladium-catalysed asymmetric hydro-acylation of 1-pentene in dichloromethane with the chiral Josiphos ligand (SL-J008-1, L**1**) was investigated. The highest ee value (73%) for the desired product 4-methyl-5-decanone (**1**) was obtained at the lowest temperature in the range (30 °C). The selectivity for **1** was between 12 and 20 mol % at 30 °C, though considerably higher at 90 °C (59 mol %). Statistical modeling was applied to quantify the influence of the process conditions on the product selectivity and ee.

INTRODUCTION

The enantioselective production of linear α-substituted ketones is of particular interest as this structure element is present in many drugs and pheromones.[1,2] A known method for the asymmetric synthesis of α-methyl substituted ketones is the reduction of α-methylene ketones by the use of Baker's yeast (Scheme 1).[3−5] Good results were obtained in, for example, the

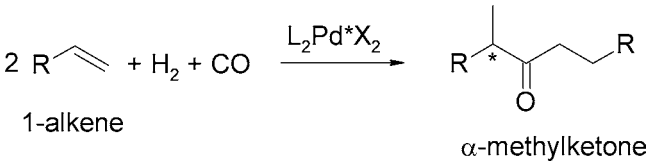
Scheme 1. Reduction of methyleneketones by Baker's yeast



reduction of α-methyleneketone with R_1 = Me and R_2 = *n*-hexyl at 30 °C. A conversion of 70% was obtained after 2 h with a product ee > 99%.[5]

An attractive alternative for the synthesis of α-methyl-substituted ketones is the hydro-acylation of 1-alkenes with Syngas (Scheme 2). Recently, Drent and Budzelaar reported a

Scheme 2. Hydro-acylation of 1-alkenes to α-methylketones



nonasymmetrical version of this reaction, using palladium diphosphine catalysts of the type L_2PdX_2 (in which X is a non-coordinating anion) for the selective production of mono-ketones (Scheme 2).[6,7] Very promising results were obtained with a catalyst prepared in situ from $Pd(OAc)_2$, an alkyl-diphosphine like DnBPP (1,3-bis(di-*n*-butylphosphino)-propane), and trifluoromethanesulphonic acid (HOTf). For 1-octene, a chemoselectivity of 98 mol % was obtained when the reactions were performed in diglyme at 125 °C with a $P_{CO} = P_{H_2} = 30$ bar.[6,7]

Our research activities concern the development of an asymmetric version of the hydro-acylation reaction given in Scheme 2. We have performed an extensive catalyst screening study with homogeneous palladium catalyst of the type $(L_2)Pd(OTf)_2$.[8] A total of 16 diphosphine ligands belonging to four different chiral ligand classes (Josiphos, DuPhos, Walphos, and ferroTANE) were studied (Figure 1). The reactions were carried out in dichloromethane at reaction temperatures between 60 and 125 °C and at initial H_2 and CO pressures of 30 bar each. The enantio-, chemo-, and regioselectivity of the reaction are a clear function of the diphosphine ligand (Table 1). Low ee values (<20%) were obtained for the Duphos ligands, albeit at a product selectivity >66 mol %. The highest ee for **1** was 39% for a Josiphos type ligand (L**1**) (Figure 1) at 60 °C, though the product selectivity was low (6 mol %). Other products were enones, higher CO−olefin oligomers resulting from alternating CO−olefin copolymerisation aldehydes/alcohols resulting from hydroformylation and olefin oligomerisation products (Scheme 3).

In this paper, we have investigated the effects of process conditions such as temperature and H_2/CO pressure on the hydro-acylation reaction of 1-pentene with chiral ligand L**1**, with the objective to optimise the chemo-, regio-, and enantioselectivity. Statistical modelling software (Design Expert) has been used to investigate and quantify the influence of these process conditions on reaction performance.

EXPERIMENTAL SECTION

Chemicals. Josiphos ligand L**1** ((R,S)-SL-J008-1), was purchased from Sigma Aldrich (≥97%). The ligand and palladium acetate (Sigma Aldrich >98%) were stored in a glovebox. Dichloromethane (Lab-Scan 99.8%) was distilled from CaH_2 before use and stored under nitrogen. 1-Pentene (Sigma Aldrich 98%) was distilled from sodium and stored under nitrogen.[9,10] Trifluoromethanesulfonic acid (HOTf) (Strem 99+%) was stored under nitrogen at 5 °C. The synthesis gas

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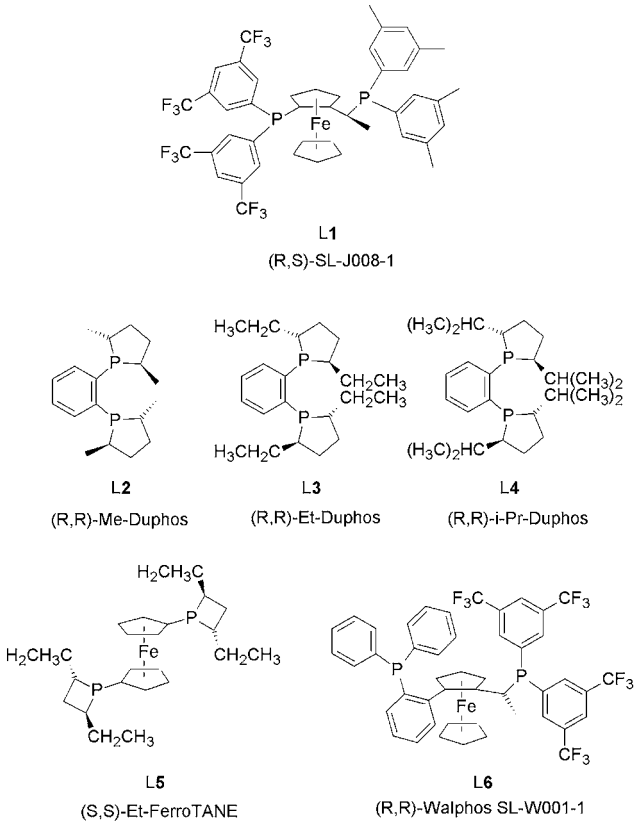

Figure 1. Overview of chiral diphosphine ligands tested for the hydroacylation of 1-pentene.

used was a 50:50 premixed CO/H_2 gas mixture (HiQ (high quality), CO ≥ 99,997 vol%, H_2 ≥ 99.9999 vol%) and was purchased from Hoek Loos. Pure hydrogen gas was also obtained from Hoek Loos (HiQ, purity ≥99.9999 vol%). Racemic 4-methyl-5-decanone was synthesised using literature procedures.[4,11] Enantio-enriched (80% ee) 4-methyl-5-decanone was synthesised in a four step procedure.[4,11] Enantio-enriched 4-methyl-nonanone (90% ee) was prepared using a three step procedure.[4,12] The tail-to-tail monoketone, 6-undecanone (**2**), was purchased from Sigma Aldrich (97%).

Experimental Setup. 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 2). The maximum operating pressure of the reactor was 200 bar, the maximum temperature 200 °C. The reactor was electrically heated and the reactor content stirred by a Parr overhead stirrer, equipped with a gas inducing impeller. Temperature and stirring speed were controlled by the Parr 4843 controller. The synthesis gas was fed from a premixed (50/50) gas cylinder and additional hydrogen was added manually from a separate gas cylinder.

General procedure. The catalyst was freshly prepared before each experiment under a nitrogen atmosphere using standard Schlenk techniques. $Pd(OAc)_2$ (9 mg, 0.04 mmol) was dissolved in dichloromethane (2 mL). After approximately 10 min the diphosphine ligand **L1** (0.04 mmol) dissolved in dichloromethane (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 min before use. The batch autoclave was charged with solvent (dichloromethane, 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 (10−100 bar) with synthesis gas (50/50 H_2/CO), and when required, H_2 (10−140 bar) was added. Subsequently, the reactor was heated to the desired reaction temperature (30, 60, or 90 °C). During reaction, the stirrer speed was maintained at 1000 rpm. After 5 h, the reactor was cooled to room temperature, depressurised, and flushed several times with N_2. The liquid product was filtered over silica gel to remove the catalyst.

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 min at 30 °C, from 30 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.[14] The method was applied for peaks belonging to the most abundant product groups present in the samples: mono-oxygenates (ketones, aldehydes/alcohols), olefin dimers and trimers, 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 (eq 1).[15]

$$X_j = \frac{F_j/(\sum C_{ef})_j}{\sum_i^n (F_i/(\sum C_{ef})_i)} \quad (1)$$

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.[16]

Table 1. Overview of results for catalytic hydro-acylations of 1-pentene using the examples of chiral Josiphos, Duphos, FerroTANE, and Walphos ligands[a,b]

entry	ligand[c]	sat. MK (1 + 2 + 3) (%)[d]	sat. MK (1) (%)[e]	S_{MD}[f]	ee[g]	sat. MK (2) (%)[e]	enones (4) (%)	alc/ald (8 + 9) (%)	DK (5) (%)	dim. (6) (%)	olefin conv (%)
1	L1	44	13	6	39	87	23	0	32	0	59
2	L2	69	95	66	16[h]	5	4	1	17	0	58
3	L3	59	96	57	20[h]	4	2	0	34	0	32
4	L4	42	100	42	6	0	16	0	37	0	72
5	L5	16	44	7	4	56	48	1	27	0	39
6	L6	15	47	7	6	53	36	0	24	15	73

[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, 60 °C. [b]Numbering of compounds is given in Scheme 3. [c]Ligand numbering is provided in Figure 1 [d]H-to-h regioisomer (**3**) was below the GC detection limit. [e]In the sat. MK fraction (**1**+**2**+**3**). [f]Defined according to eq 3. [g]Ee of the saturated h-to-t monoketone, 4-methyl-5-decanone (**1**). [h]Actual value likely lower due to peak overlap in GC measurements.

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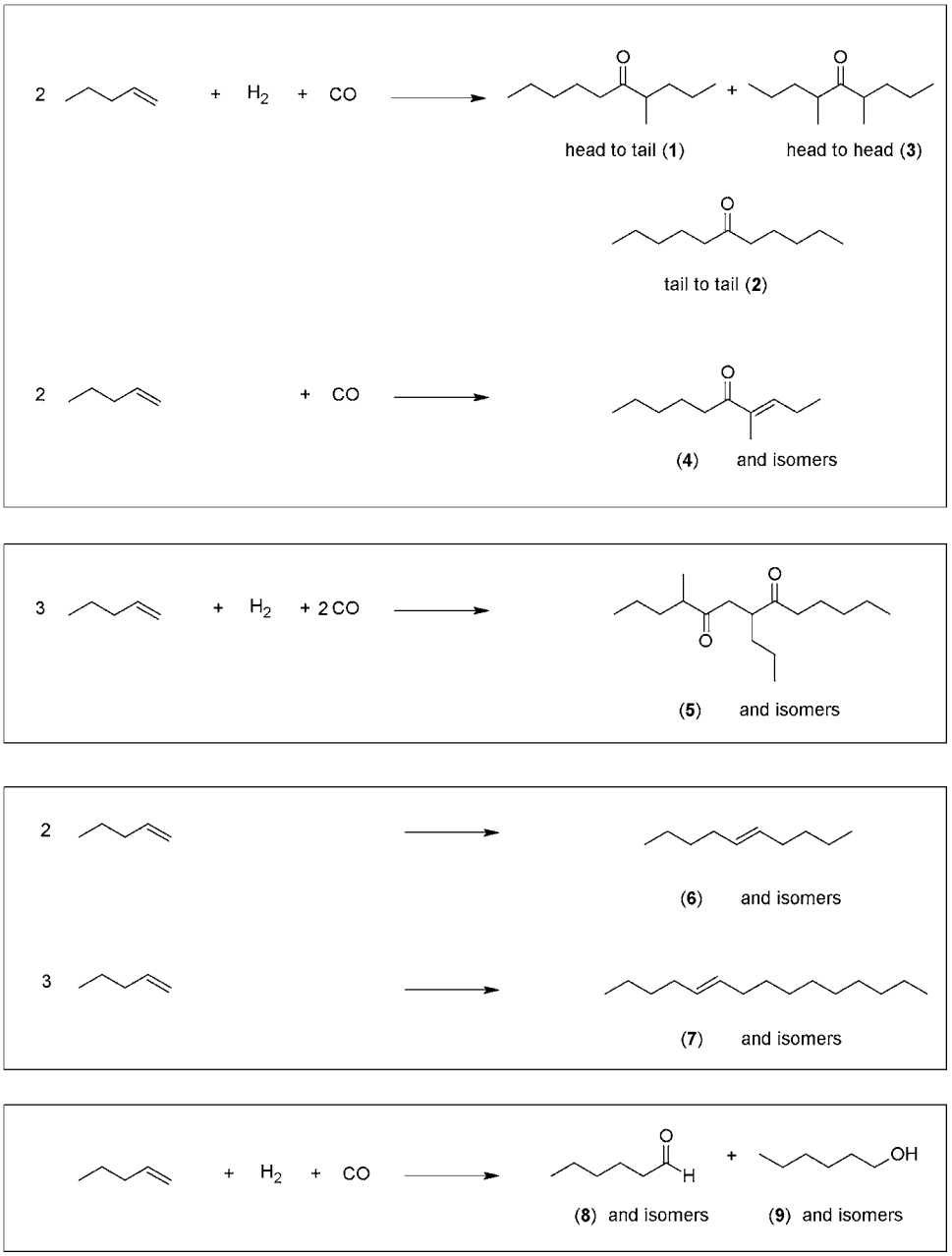
Scheme 3. Main- and side products from the L_2PdX_2-catalyzed reactions of 1-pentene with Syngas (only one isomer of the products is shown)



The 1-pentene conversion was determined using the same GC equipment. 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 to 250 °C, rate 5 °C/min, final time 10 min.). GC chromatograms were recorded on a GC-FID HP-5890 series II, with FID on 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 of the desired 4-methyl-5-decanone (**1**) 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: 50 to 55 °C, rate 10 °C/min, hold time 100 min, then from 55 to 180 °C, rate 10 °C/min, final time 15 min. A solvent change was required before the reaction products could be injected. For this purpose, the dichloromethane was removed under reduced pressure (100 mbar, 30 °C) to give a yellow oil. The oil was redissolved in diethyl ether and analysed. The retention times of the enantiomers were 107.9 and 108.3 min. 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-product of the reaction. Also the chromatograms were compared with those obtained with the reference materials.

Statistical Modeling Using Design Expert. The experimental results for each response were analyzed using

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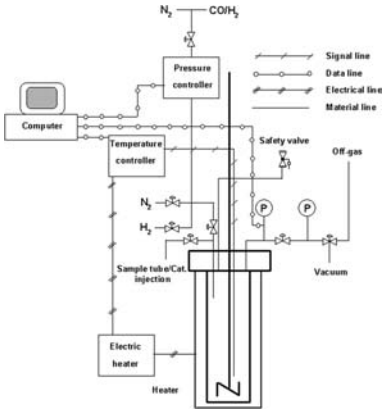

Figure 2. Schematic representation of the reactor setup.

the Design Expert 7 software package. Responses are modeled using standard expressions (eq 2):

$$y = b_0 + \sum_i b_i x_i + \sum b_{ii} x_i^2 + \sum_j \sum_k b_{jk} x_i x_k \quad (2)$$

Here, i = A to C, j = A to C, and k = A to C with A, B, C representing the independent variables; bi, bii, and bjk are the regression coefficients which are obtained by statistical analyses of the data. Significant factors were selected on the basis of their p value in the ANOVA analyses. Factors with a p value lower than 0.05 are regarded as significant and included in the response model. Backward elimination was applied to eliminate all statistically insignificant terms. After each elimination step, a new ANOVA table was generated to select the subsequent nonsignificant factor.

RESULTS

Experimental Window and Approach. A total of 10 experiments was carried at different process conditions (temperature and partial CO and hydrogen pressure) using an in situ formed Pd-catalyst based on $Pd(OAc)_2$, Josiphos ligand L**1** and HOTf as the acid component in dichloromethane. The experimental ranges for the independent variables are given in Table 2.

Table 2. Experimental ranges for the hydro-acylation of 1-pentene

	lowest value	highest value
T (°C)	30	90
P_{CO} (bar)	2.5	30
P_{H_2} (bar)	17.5	105

For all experiments, a fixed Pd intake was applied and the substrate to catalyst ratio was set at 910 (about 0.1 mol %). For each experiment, the olefin conversion, product distribution and the ee of the desired 4-methyl-5-decanone (**1**) was determined and the results are given in Table 3. Here, the selectivity for **1** (S_{MD}, mol %) is defined as follows:

$$S_{MD} = (\text{amount of saturated monoketones } (\mathbf{1} + \mathbf{2} + \mathbf{3})) \times (\text{fraction of } (\mathbf{1}) \text{ in saturated monoketones}) = \frac{C_1}{\sum C_{\,all\ products}} \quad (3)$$

The responses (ee, conversion, S_{MD}, chemo- and regioselectivity) at different process conditions were analysed using statistical software to obtain a quantitative relation between the responses and the process variables.

Effect of Process Conditions on the ee of 1. The ee of **1** is a strong function of the temperature. Highest ee values were obtained at 30 °C (67−73%, see Table 3). At a reaction temperature of 90 °C (Table 3, entry 1 and 2) the ee was negligible. A verification experiment was performed with the other enantiomer (*S*,*R*) of Josiphos ligand L**1** at 30 °C. In this case, the opposite enantiomer of **1** was obtained with an ee of 67%, which is within the experimental error. The GC chromatograms for both experiments are given in Figure 3.

The effect of the process conditions on the ee was quantified using statistical modelling. It was found that only the temperature and neither the hydrogen nor the CO partial pressure has a significant effect on the ee, leading to the following relation:

$$\text{ee} = 103 - 1.14 \times T \quad (4)$$

Clearly a low temperature has a positive effect on product ee. A parity plot for the predicted and experimental ee values using this equation is given in Figure 4, indicating that agreement between model and experimental data is good (adjusted R^2: 0.973).

Selectivity for 4-Methyl-5-decanone (S_{MD}) as a Function of Process Conditions. Statistical modeling of the data reveals that the S_{MD} is a function of both the reaction temperature and the partial CO pressure (eq 5). The effect of hydrogen pressure is not significant.

$$S_{MD} = -13 + 0.81 \times T - 0.90 \times P_{CO} \quad (5)$$

Thus, low partial CO pressures and higher reaction temperatures have a positive effect on S_{MD}. This is also illustrated in Figure 5, where the S_{MD} is provided as a function of the CO pressure and the reaction temperature. The highest selectivity (60 mol %) was obtained at a temperature of 90 °C and a P_{CO} of 5 bar.

Agreement between the model data and experimental data is adequate (adjusted R^2: 0.910), as is also illustrated by the parity plot given in Figure 6. Evidently, it is desired to identify those process conditions that lead to **1** with a high product selectivity and enantioselectivity. Unfortunately, these conditions appear to be conflicting. The highest ee is obtained at low temperature, whereas the highest selectivity to **1** is observed at the highest temperature in the range.

Chemoselectivity vs Process Conditions. The S_{MD} is a function of both the chemo- and regioselectivity of the hydro-acylation reaction. To gain insight in the extent to which the two factors influence the S_{MD}, the effect of process conditions on the chemo- and regioselectivity were evaluated separately.

The highest chemoselectivity with respect to saturated monoketones was obtained at 90 °C (Table 3, entry 2: 83% saturated monoketones). The major byproduct are enones (**4**, 2−37 mol %), diketones (**5**, 2−32 mol %) and olefin dimers (**6**, 0−80 mol %) and trimers (**7**, 0−17 mol %). Aldehydes (**8**) and/or alcohols (**9**) formation by hydroformylation was observed for only two experiments (maximum 2 mol %). The 1-pentene dimers and trimers (Scheme 3) are monounsaturated (GC−MS) though the position of the double bond and the extent of branching could not be established.

The effect of process conditions on the desired saturated monoketone fraction in the product mixture is best described by the following relation (adjusted R^2: 0.880):

$$F_{sat.MK} = -13 + 1.08 \times T - 0.65 \times P_{CO} \quad (6)$$

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Table 3. Effects of process conditions on conversion, chemo-, regio-, and enantioselectivity for the hydro-acylation of 1-pentene[a,b]

entry	T (°C)	P_{CO} (bar)	P_{H_2} (bar)	sat. MK (**1**+ **2** + **3**) (%)[c]	sat. MK (**1**) (%)[d]	S_{MD}[e]	ee[f]	sat. MK (**2**) (%)[d]	enones (**4**) (%)	alc/ald (**8** + **9**) (%)	DK (**5**) (%)	dim. (**6**) (%)	trim. (**7**) (%)	olefin conv (%)
1	90	30	30	61	56	35	0	44	29	1	8	0	0	64
2	90	5	105	83	72	60	0	28	7	0	7	0	0	84
3	60	30	30	44	13	6	39	87	24	0	32	0	0	59
4	60	5	50	43	50	22	29	50	22	0	21	10	0	81
5	60	15	105	55	50	27	41	50	23	1	19	0	0	50
6	60	15	145	44	41	18	32	59	18	0	15	20	2	77
7	60	30	120	20	55	11	33	45	37	0	21	19	2	90
8	30	5	50	20	55	11	67	45	7	0	11	43	17	22
9	30	2.5	50	18	62	11	65	38	2	0	6	62	10	59
10	30	2.5	17.5	12	84	10	73	16	2	0	2	80	4	24

[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, dichloromethane. [b]Numbering of compounds is given in Scheme 3. [c]H-to-h regioisomer (**3**) was below the GC detection limit. [d]In the sat. MK fraction (**1**+**2**+**3**). [e]Defined according to eq 3. [f]Ee of the saturated h-to-t monoketone, 4-methyl-5-decanone (**1**).

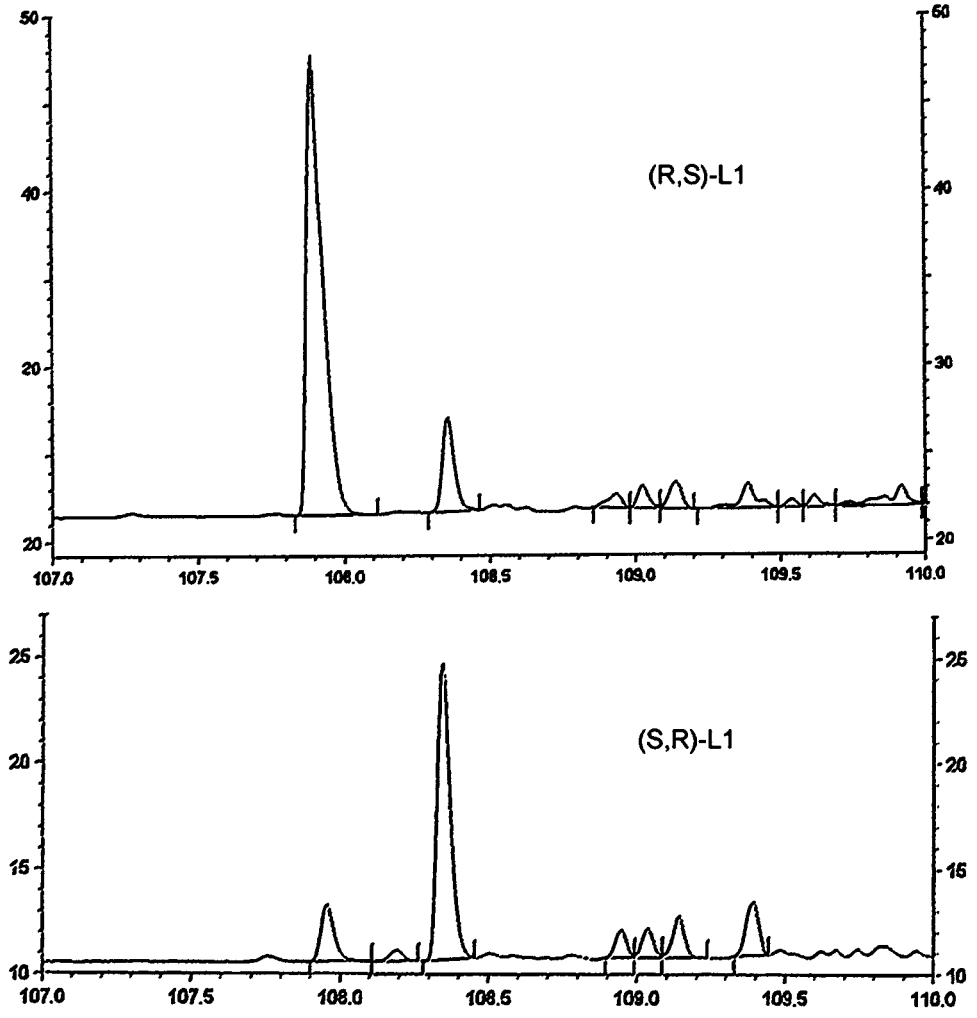

Figure 3. Chiral GC chromatograms of the experiment performed at 30 °C, P_{CO} = 2.5 bar and P_{H_2} = 17.5 bar with (*R*,*S*)-L**1** and (*S*,*R*)-L**1**.

The effect of hydrogen pressure is statistically not relevant. The relation is visualised in Figure 7, a parity plot is provided in Figure 8. Higher reaction temperatures have clearly a positive effect on the amount of saturated monoketone formed. The effect of the P_{CO} is less pronounced, though higher partial CO pressures have a small but significant negative effect on the saturated monoketone selectivity.

For some of the reactions, olefin dimers and trimers were actually the main products (Table 3). The amount of olefin dimers in the mixture was modeled as a function of process conditions and is best described by the following relation:

$$F_{dim} = 85 - 0.96 \times T - 0.52 \times P_{CO} \quad (7)$$

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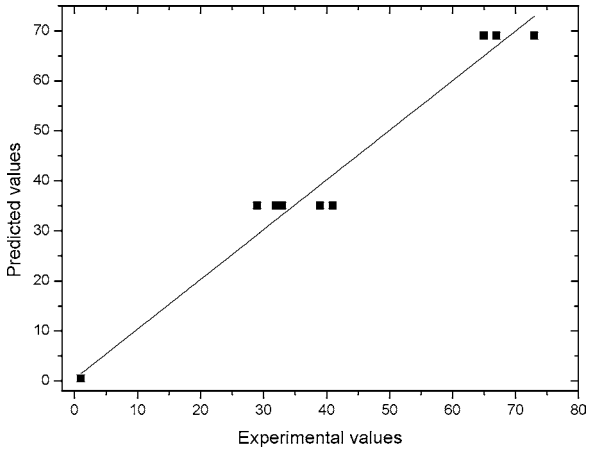

Figure 4. Experimental versus modeled ee values using eq 4.

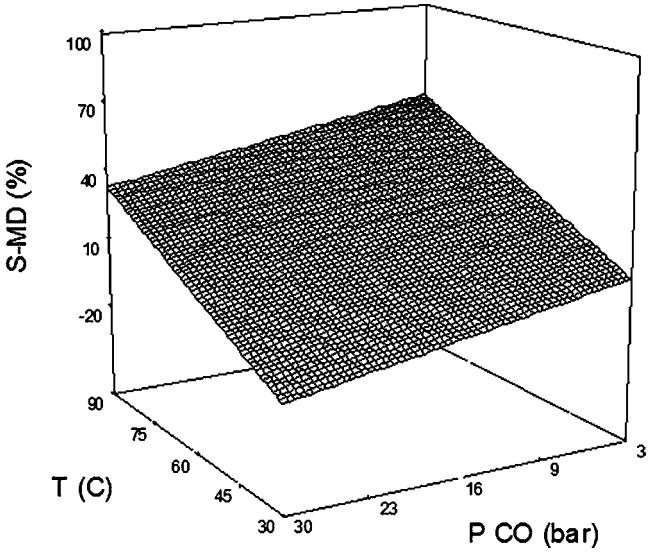

Figure 5. Selectivity towards **1** (S_{MD}) versus reaction temperature and partial CO pressure (H_2 fixed at 80 bar).

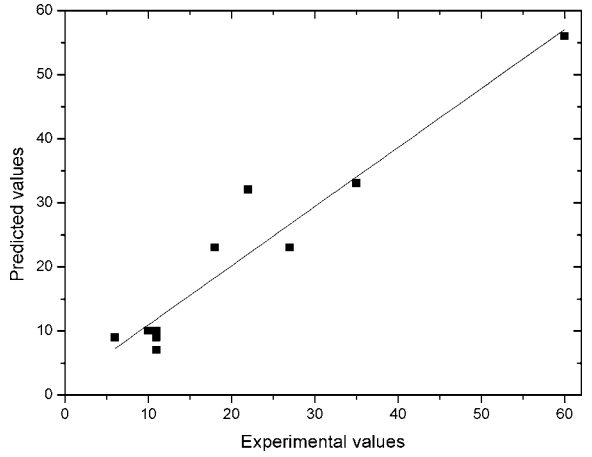

Figure 6. Predicted selectivity for (**1**) versus the experimental values.

The relation is visualised in Figure 9. Clearly, the temperature has a pronounced effect on the amount of dimerization products, with lower temperatures leading to high amounts of dimers. The amount of dimers is also a function of the partial

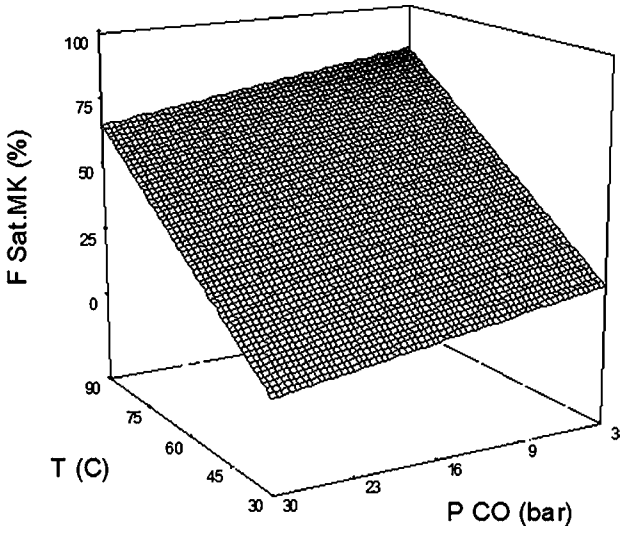

Figure 7. Chemoselectivity towards saturated monoketones (**1** + **2** + **3**) versus reaction temperature and P_{CO} (P_{H_2} = 80 bar).

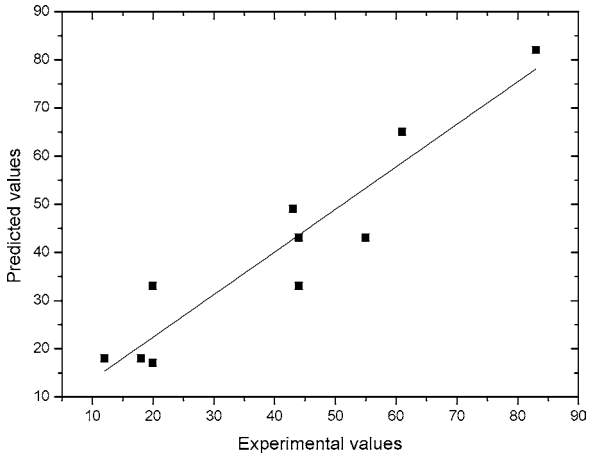

Figure 8. Experimental versus predicted values for the chemoselectivity of the saturated monoketone fraction (**1**+**2**+**3**).

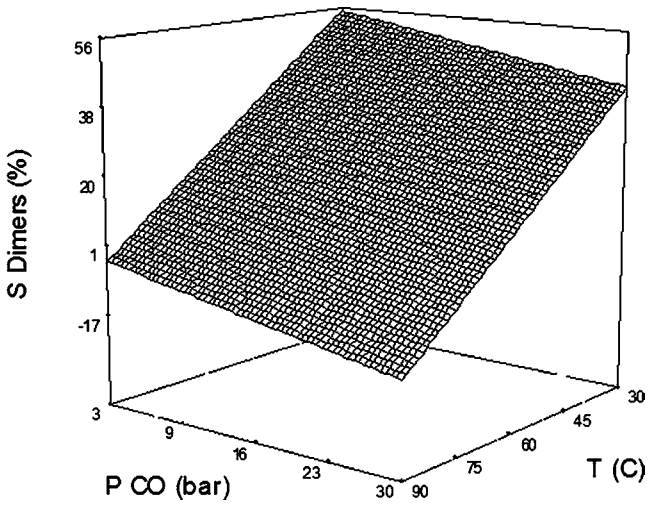

Figure 9. Modeled amount of olefin dimerization products (**6**) as a function of process conditions (eq 7).

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CO pressure, with high pressures leading to a reduction in the amount of dimerization products.

Regioselectivity. The major regioisomers present in the saturated monoketone fraction were the head-to-tail (**1**) and the tail-to-tail isomer (**2**), whereas the head-to-head regioisomer (**3**) could not be detected (GC). It turned out to be impossible to determine statistically sound relations between the process conditions and the amount of the desired head-to-tail regioisomer in the reaction mixture. However, in the majority of the experiments, the desired head-to-tail isomer is formed in the largest amounts.

Olefin Conversion. The highest 1-pentene conversion after 5 h was 90%, obtained at 60 °C, a partial CO pressure of 30 bar and a partial H_2 pressure of 120 bar (Table 3). This corresponds to an average turnover frequency (TOF) of 160 mol/(mol Pd·h). The TOF at the initial stage of the reaction is expected to be considerably higher as the TOF reported here is an average over the batch time. Typical literature values for achiral hydro-acylations using alkyldiphosphines in batch reactors 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.[6,7] Thus, particularly considering the relatively low temperature, the TOF for the Josiphos-based catalyst is at the high end of the range given in the literature.

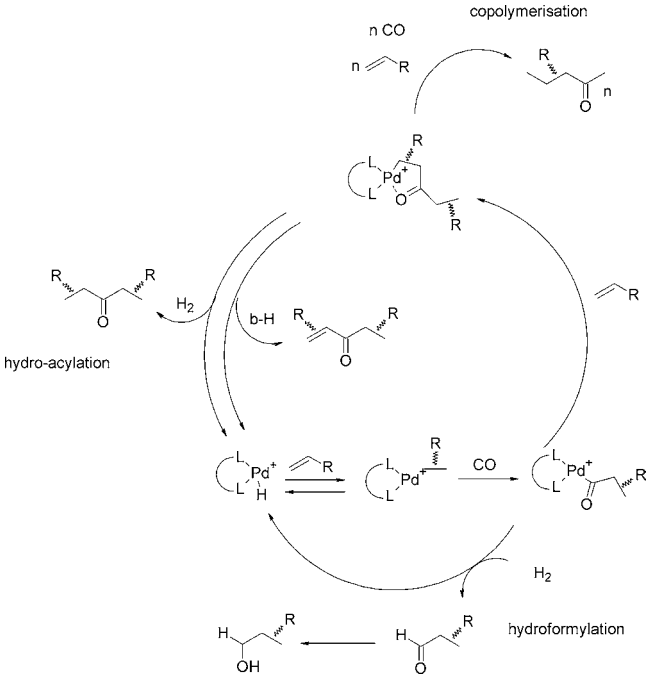
A sound statistical relation for the effects of process conditions on the 1-pentene conversion could not be obtained. One of the possible reasons is the simultaneous occurrence of 1-pentene isomerisation to mixtures of internal olefins (GC analyses of the reaction mixture). It is well-known that the activity of L_2PdX_2 catalysts for internal olefins is much lower than for α-olefins.[6,7] The extent of olefin isomerisation will also be affected by process conditions, though to a different extent than hydro-acylation, leading to a complex relation between olefin conversion and process conditions. Furthermore, isomerisation is a reversible process and the internal olefins may isomerise back to 1-pentene and converted to hydro-acylation products.

DISCUSSION

The hydrocarbonylation of olefins using $(L_2)PdX_2$ catalysts leads to the formation of the desired monoketones (hydro-acylation) as well as to alcohols and aldehydes by hydro-formylation and higher ketones by copolymerisation reactions.[6,7] A proposed catalytic cycle including the formation of the various product classes is given in Scheme 4. The active species is commonly accepted to be a square-planar cationic Pd-hydride complex.[6,7]

Chemoselectivity. The major product classes formed using Josiphos ligand L**1** in dichloromethane are saturated monoketones, enones, diketones and noncarbonylation products like olefin dimers and trimers (Scheme 3 and Table 3). Aldehydes/alcohols were not formed in significant amounts under these conditions (<2 mol %). This suggests that the key intermediate in the catalytic cycle is the Pd-alkyl species with a chelating carbonyl group (top compound in catalytic cycle, Scheme 4). This compound may either react with hydrogen to form the desired saturated monoketones, undergo β-hydrogen elimination to produce enones or react with CO and subsequently an olefin to give a diketone. Apparently, all three pathways occur when using L**1**. The selectivity towards the desired saturated monoketones is shown to be a function of the temperature and to a lesser extent the CO pressure (eq 6), whereas the effect of the hydrogen pressure was statistically not relevant. Higher temperatures and lower CO pressures were shown to

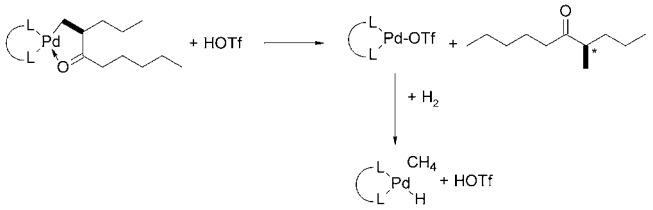
Scheme 4. Proposed catalytic cycle for the Pd(II)-catalysed reactions of 1-alkenes and syngas



favor the formation of saturated monoketones. Higher CO pressures are expected to speed up the rate of CO insertion in the Pd-alkyl bond. This reaction is known to be reversible and only a subsequent olefin insertion will produce a stable Pd-alkyl compound. The latter is subsequently hydrogenated to form a ketone.

The observation that the hydrogen pressure does not affect the chemoselectivity is rather surprising. On the basis of Scheme 4, it is anticipated that higher hydrogen pressures would lead to higher amounts of the saturated monoketones at the expense of enone formation. However, this is not the case. This is an indication that hydrogen is not directly involved in the formation of saturated monoketones from the Pd-chelate. A possible alternative termination mechanism without direct hydrogen involvement is the reaction of the Pd-chelate with HOTf, present in excess in the reaction mixture, to give a $L_2Pd(OTf)_2$ species and the saturated monoketone (protonolysis). Subsequent reaction of the $L_2Pd(OTf)_2$ with hydrogen then leads to the regeneration of the Pd−H and HOTf (Scheme 5).[17] Termination reactions by protonolysis are

Scheme 5. Alternative termination mechanism: Pd-alkyl protonolysis with HOTf



well-known in CO-olefin copolymerisations. For instance, Vavasori and co-workers reported the active involvement of acetic acid in the termination reaction in the ethylene/CO copolymerisations catalysed by $PdCl_2$(dppf) complexes.[18]

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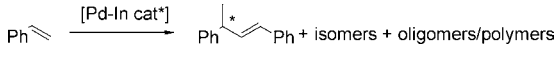
Remarkable is the formation of 1-pentene oligomers under hydro-acylation conditions. The formation of olefin dimerization products in the absence of CO with the L_2PdX_2 catalyst used in this study is well-known in the literature. Early examples of the dimerization of linear α-olefins were reported by Drent (1990)[19] and Jiang et al. (1993).[20] In 2003, Tsuchimoto et al.[21] demonstrated that palladium−indium triflate catalysts were highly active for the dimerization of vinylarenes. More recently, Bedord et al.[22] developed an (asymmetric) version by using $Pd(OAc)_2$, and a chiral diphosphine ligand in the presence of $In(OTf)_3$ (Scheme 6). Josiphos ligands were also shown to be active for the reaction.

Scheme 6. Styrene oligomerisation catalysed by $Pd(AcO)_2$/diphosphine ligand/$In(OTf)_3$ catalyst systems



A possible explanation for olefin oligomerisation is the (strong) acid-catalysed (here HOTf) oligomerisation of 1-pentene. If this would be valid, however, olefin oligomerisation is expected to occur for all reactions and this is certainly not the case (Table 3). 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 (Scheme 4). When this explanation is valid, higher amounts of olefin dimers are expected at low CO pressures. This was indeed observed experimentally and supported by statistical modelling (Figure 9). Though not conclusive, a mechanism involving Pd-compounds for 1-pentene oligomerisation is likely. Further research will be required to provide definite conclusions on the formation of olefin oligomers.

Regioselectivity. The major regioisomers present in the saturated monoketone fraction were the head-to-tail (**1**) and the tail-to-tail isomers (**2**), whereas the head-to-head regioisomer (**3**) could not be detected (GC). It proved not possible to determine statistically sound relations between the process conditions and the amount of the desired head-to-tail regioisomers in the reaction mixture. However, in the majority of the experiments, the desired head-to-tail isomer is formed in the largest amounts.

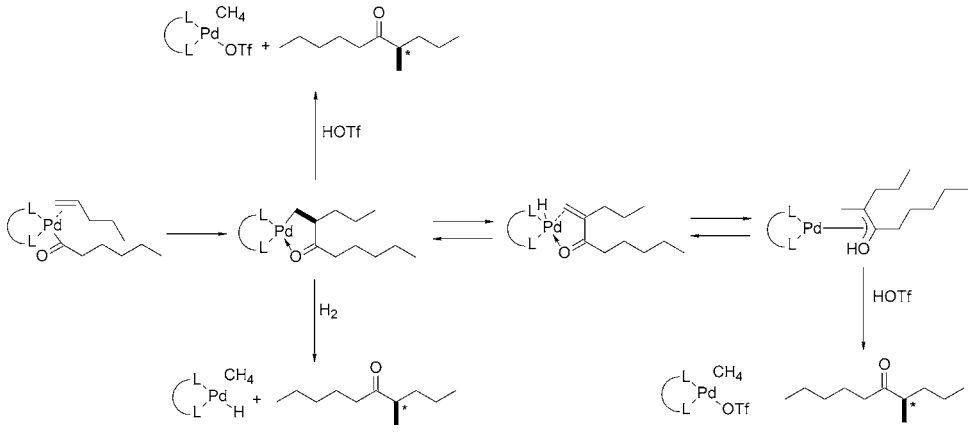
Enantioselectivity. The enantioselectivity was shown to be a strong function of the temperature (eq 4), whereas the P_{CO} and P_{H_2} have no significant effect on the product ee within the experimental ranges. This gives valuable information on the origin of enantioselectivity of the hydro-acylation reaction. The enantioselectivity of the reaction is most likely determined by the second insertion of the olefin in the Pd-alkyl bond of the chelate (Scheme 4).[8] To obtain enantiopure **1**, the insertion step should be highly stereoselective. Lower ee values may be explained by either an intrinsically limited chiral induction of the Josiphos ligand or by partial epimerization of the stereogenic centre after the second olefin insertion step (Scheme 7).

In the case the ee is only affected by the intrinsic properties of the Josiphos ligand, the partial pressures of CO and hydrogen are not expected to affect the product ee, as was observed experimentally. However, this does not exclude the occurrence of epimerization. Epimerization can occur by (reversible) β-hydrogen elimination followed by conjugate hydride addition and formation of the palladium enolate.[23] In this case, the product ee is not only determined by the intrinsic chiral induction during the olefin insertion step but is also a function of the rate of β-hydrogen elimination/enolisation versus the rate of the termination reaction of the Pd-chelate with either HOTf or hydrogen (Scheme 7). The termination reaction with hydrogen is less likely as the amount of saturated monoketones in the mixture was found to be independent of the hydrogen pressure (*vide supra*). Thus, the rate of termination by protonation versus the rate of β-hydrogen elimination likely affects the rate of epimerization. When this mechanism is valid, the product ee is expected to be independent of the hydrogen pressure and this was indeed the case. Further research including molecular modeling is required to gain further insight into the occurrence of epimerization and its role in the enantioselectivity of the reaction.

■ CONCLUSIONS

The effect of process conditions (temperature, partial CO and hydrogen pressure) on the synthesis of enantio-enriched **1** by the Pd-Josiphos L**1**-catalysed reaction of 1-pentene with syngas was established. The selectivity of the reaction (S_{MD}) was shown to be a function of the temperature and the highest amounts of **1** were obtained at the highest temperature in the range (90 °C). The product ee is also strongly temperature depending, with lower temperatures leading to higher ee values. The highest ee of 73% was found at 30 °C. As the requirements for high chemoselectivity and enantioselectivity are clearly conflicting, a high yield synthesis of enantiopure **1** with the Josiphos ligand used in this study remains elusive. Such studies

Scheme 7. Epimerization of the stereogenic centre leading to ee reductions



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with alternative bidentate chiral ligands are in progress and will be reported in due course. The effects of process conditions were quantified using statistical modelling. The results provide interesting mechanistic insights in the effects of process conditions on the chemo-, regio-, and enantioselectivity of (asymmetric) hydro-acylation reactions.

AUTHOR INFORMATION

Corresponding Author
*H.J.Heeres@rug.nl

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