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Hydroformylation of Internal Alkenes to Linear Aldehydes: a Review

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Lead-in. In 2003 hydroformylation celebrated its 65th anniversary. In these years hydroformylation has emerged as one of the most important transformations in the field of homogeneous catalysis. Intensive research by industry and academia led to remarkable results concerning simultaneous control of reactivity and selectivity, but still many aspects of hydroformylation have not been completely elucidated. Fast and selective conversion of less reactive, internal and higher functionalised alkenes is of great importance, but still requires a satisfactory solution despite various research efforts in the past decades. This article reviews the progress toward the development of cobalt-, rhodium-, platinum- and palladium-based catalysts for the selective conversion of internal alkenes to linear aldehydes.
1. Introduction.

Like many landmark discoveries, hydroformylation was discovered serendipitously. In 1938, while investigating the intermediacy of alkenes in Fischer-Tropsch reaction, Otto Roelen discovered that alkenes were converted into linear and branched aldehydes by applying a cobalt-containing heterogeneous catalyst under a carbon monoxide and dihydrogen atmosphere (Scheme 1). The actual catalyst turned out to be the in situ generated homogeneous HCo(CO)$_4$ complex. Ever since, this clean and mild method for the functionalisation of hydrocarbons has grown to be among the most important homogeneously catalysed reactions in industry covering an annual production of 8 million tons of various aldehydes and alcohols for the manufacture of detergents, soaps, and plasticiser alcohols. 2-Ethylhexanol, produced by $n$-selective hydroformylation of propene, followed by aldol condensation and subsequent reduction, has been the main product of hydroformylation. For higher alkene hydroformylation, linear products are preferred over the branched ones because of their assumed better biodegradability, but highly branched products are often desirable for their properties, e.g. as lubricating oil additives in order to depress the freezing point of the oil.

Cobalt and rhodium complexes constitute the most important catalysts for hydroformylation, but the use of other metals, like Pt, Pd, Ir, Ru and Fe has also been reported.

A target of great interest in hydroformylation chemistry is the selective conversion of less reactive internal and functionalised alkenes to linear aldehydes. Interesting industrial applications would be: 1) the hydroformylation of Raffinate II, a mixture of butenes obtained during the Naphtha-steamcracking, to linear aldehydes, 2) the preparation of high-value-added oleochemicals (e.g. fatty acid derivatives bearing an additional functional group) obtained by the hydroformylation of (internally) unsaturated fatty acids, and 3) the hydroformylation of alkyl 3-pentenoate, 3-pentenoic acid or 3-pentenenitrile that lead to products that can be used in the production of $\varepsilon$-caprolactam or adipic acid, which are precursors for respectively nylon-6 and nylon-6,6. To achieve this goal a catalyst is required that shows a high isomerisation activity since the thermodynamically less stable terminal alkenes have to be formed prior to hydroformylation. Cobalt catalysts are particularly suited for this reaction owing to the low hydroformylation activity and high isomerisation activity (vide infra). The low reactivity of cobalt catalysts necessitates high temperatures and thus high pressures, but unfortunately this also leads to hydrogenation and formation of heavy end-products via aldol condensation. In hydroformylation

\[ \text{Scheme 1 Hydroformylation.} \]
chemistry the elimination of the disadvantages of Co-based systems is one of the current demands, e.g. by novel catalysts or technologies that lead to higher activities, regio-selectivities, and that show a better functional group tolerance. Rhodium catalysts are particularly suited as they combine all these aspects, but they hardly show any isomerisation activity, which renders them unsuitable for the hydroformylation of internal alkenes. In the last two decades many processes based on cobalt have been replaced by rhodium, especially for the hydroformylation of short chain alkenes, but for higher alkenes, and especially for the hydroformylation of internal higher alkenes, there exists no good alternative and thus cobalt-based catalysts are still preferred.

In this review we focus on catalyst development of the hydroformylation of internally unsaturated compounds to linear aldehydes. In particular rhodium catalysts have undergone a remarkable development, while cobalt catalysts have remained more or less unchanged over the years, and palladium has just been recognised as a suitable transition metal for hydroformylation.

1.1 Mechanistic considerations.

The generally accepted dissociative mechanism of the phosphine modified rhodium catalysed hydroformylation, first proposed by Wilkinson et al., is depicted in Scheme 2. The catalytic cycle begins with ligand dissociation (either CO or a phosphorus donor ligand) from the bis(phosphine) dicarbonyl rhodium hydride 1, which is the most commonly observed catalyst resting state, to form the 16 electron coordinatively unsaturated rhodium intermediate 2. After alkene association (3), hydride migration takes place to form either a linear or branched alkyl rhodium intermediate (4 and 4'). With the formation of the branched alkyl rhodium intermediate a new chiral centre is created, which is important for asymmetric hydroformylation. CO association to 4 or 4' followed by alkyl migration (also referred to as migratory insertion of CO) yields the unsaturated four coordinated acyl rhodium intermediate 6 and 6', respectively. Hydrogenolysis (by oxidative addition of dihydrogen or via bi-metallic mechanism (not depicted in Scheme 2)) leads to the formation of the respective aldehydes and regeneration of rhodium intermediate 2. Only in few cases hydrogenolysis is rate determining (Type II kinetics) and species 7 and 7' can be observed as catalyst resting state after respective association of CO to 6 and 6'.

The most dominant side reaction of hydroformylation is isomerisation, which proceeds often via \( \beta \)-hydrogen elimination from the branched alkyl rhodium intermediate 4' to yield 8. Isomerisation can also occur through a metal induced intramolecular 1,3-hydrogen shift via a \( \eta^3 \)-allyl metal hydride (\( \pi \)-allyl mechanism), especially when transition metals of the platinum group metal, i.e. Ni, Pd or Pt, are used this isomerisation pathway is likely. Other commonly observed side-reactions include hydrogenation of
the substrate or product, and aldol condensation. The extent to which these reactions take place is highly dependent on the ligand, metal and reaction conditions employed.

1.2 Ligand parameters.

Soon after the beneficial effect of triphenylphosphine on the rhodium catalysed hydroformylation was discovered ligands with other donor atoms, like N, As, Sb, and Bi, were reported, but these were usually less effective than their respective P-ligands. A comparative study of Ph$_3$E (E = N, P, As, Sb, Bi) in the hydroformylation of 1-dodecene demonstrated the superiority of phosphine ligands. Other P-ligands
were applied with sterically demanding groups or electron withdrawing capacities that easily surpassed the results obtained with triphenylphosphine.\textsuperscript{17-21}

Tolman was the first to review ligand effects and introduced the steric parameter $\theta$, and the electronic parameter $\chi$ (Figures 1, and 2).\textsuperscript{22} For bidentate ligands Tolman extended the concept of cone-angle (Figure 3). This parameter was used as starting point for the concept of natural bite angle ($\beta_n$) (Figure 3).\textsuperscript{23}

The natural bite angle and the concomitant flexibility range, both introduced by Casey and Whiteker, have been used most extensively,\textsuperscript{24-29} and require less elaborate molecular mechanics studies compared to other parameters for bidentate ligands, like pocket angle,\textsuperscript{30} solid angle,\textsuperscript{31-33} repulsive energy,\textsuperscript{34,35} and accessible molecular surface.\textsuperscript{36} Clearly, the bite angle does not only induce steric effects, but it also induces electronic effects, because the P-M-P angle affects the binding in the complex ground state or intermediate states. Complete separation of the electronic and steric effects is nearly impossible as both parameters affect one another, especially in systems where a reaction is the resultant of going through many intermediate transition states, like in many catalytic processes. Still these parameters ($\theta$, $\chi$, and $\beta_n$) proved to be very useful to quantify steric and electronic properties of mono- and bidentate ligands, since often changes in activity or selectivity can be attributed to one or more of them.

### 2.1 Hydroformylation of internally unsaturated compounds.

For fast and selective hydroformylation of internal alkenes to linear aldehydes the association of the unreactive internal alkene, subsequent hydride migration followed by $\beta$-hydrogen elimination resulting in a double bond shift should be fast. More importantly, the rate of $\beta$-hydrogen elimination should be
several orders of magnitude faster than migratory CO-insertion from the branched alkyl rhodium complex, which would result in the formation of branched aldehydes, but should be the same order of magnitude or slower than migratory CO-insertion from the linear alkyl rhodium intermediate in order to maintain an acceptable hydroformylation activity. Thus, only in cases where the linear alkyl metal species shows preferential carbonylation and only when the rate of isomerisation is sufficiently high, linear aldehydes will be the main product when starting from internal alkenes. An additional affinity for primarily formation of linear alkyl metal species is advantageous for both the activity and the selectivity.

Most catalytic systems are not active for the hydroformylation of internal alkenes or require harsh conditions, which leads to a low selectivity. Only when highly active catalysts are used the internal alkenes can be hydroformylated under mild conditions.

2.2 Cobalt.

In the 1980’s a large change in catalyst system occurred: cobalt catalysts lost their importance and were mainly substituted by new technologies and modifications based on rhodium. Therefore, most hydroformylation studies in the last two decades were focused on other metals than cobalt, rhodium in particular. Nevertheless, cobalt catalysts, especially HCo(CO)_4 and HCo(CO)_3PR_3, are still preferred for hydroformylation of (internal) higher alkenes. Typical operating conditions comprise temperatures between 130 and 200 °C, total syngas pressures between 100 and 300 bar, and cobalt concentrations between 0.1 to 0.5 wt%. Linearity obtained with cobalt catalysts are in general low, but extensive isomerisation causes the product linearity obtained from the terminally or internally alkenes to differ only slightly, so effectively no loss of substrate occurs. For example, the HCo(CO)_4 hydroformylation of 1-pentene led to 82 % linearity under 90 bar CO, 80 bar H_2 and at 100 °C. Under identical conditions 76% linearity was obtained when using 2-pentene. The difference in isomer composition between the hydroformylation products of terminal and internal alkenes decreases as the CO-pressure decreases, but in contrast to rhodium systems (vide infra) a lower CO-pressure generally results in lower linearity, only few publications show opposite effects. One of the most important areas in cobalt catalysed hydroformylation is the concurrent isomerisation of reactants. During hydroformylation of higher terminal alkenes, hydroformylation does not only occur at the α-, and β- carbons, but also at other carbons along the aliphatic chain. Haymore, Asselt and Beck discussed the mechanisms of formation of various linear and branched aldehydes from single unsaturated reactants. For example, _C labelled 1-octene hydroformylation showed that a large amount of linear product was produced via hydroformylation of 1-octene preceeded by six consecutive double bond shifts (12% of the total amount of linear product). Two isomerisation pathways are possible. In one mechanism isomerisation occurs
via a reversible coordination-addition of the catalyst to the free alkene.⁴⁷ In an alternative mechanism, the cobalt alkene complex does not dissociate to provide free internal alkenes.⁴⁸ Extensive isomerisation of coordinated alkenes occurs; but unreacted alkenes are isomerised relatively slowly, consequently the aldehyde distributions differ slightly with conversion.⁴⁴ The latter mechanism is most commonly observed, while the former mechanism occurs when the rate of the reaction is so high that the solution is no longer saturated with CO.

The required reaction conditions for cobalt catalysts become more moderate by the use of tertiary phoshines,⁴⁸,⁴⁹ and additionally differences between product linearity starting from internal or terminal alkenes are reduced. The modified cobalt systems require lower syngas pressures to stabilise the catalyst system, but reaction rates are lower due to decreased electrophilicity of the cobalt centre, which reduces the rates of alkene coordination and CO dissociation. On the other hand, an increase in regio-selectivity and a significant increase in hydrogenation activity are observed, which results in mainly alcohol formation.¹⁰,⁵⁰ It was postulated that different Co-species are responsible for either hydrogenation or isomerisation.⁴⁶ The amount of heavy by-products is low, presumably because the concentration of aldehydes during the reaction is low.⁵⁰ Fell et al. obtained 78% product linearity of the aldehyde/alcohol mixture in the hydroformylation of trans-4-octene using 25 mol% of P(C₆H₁₁)₃ (T = 150 °C, p(CO/H₂)(1:1) = 200 bar at room temperature).⁴³ Under identical reaction conditions 80% linearity was obtained for hydroformylation of 1-octene. The unmodified system led to 55% and 65% linearity for hydroformylation of trans-4-octene and 1-octene, respectively. Hershman and Craddock reported very high regio-selectivities of 87% toward the linear alcohol for the P(n-C₄H₉)₃Co(CO)₄ catalysed hydroformylation of 1-hexene and 2-hexene at 170 °C under 27 bar of a 1:2 CO/H₂ atmosphere,⁵¹ which could be improved to 90% linearity at 140 °C under 130 bar of 1:2 CO/H₂.⁵²

Diphosphines are inefficient ligands for cobalt catalysed hydroformylation of internal alkenes,⁵³,⁵⁴ since effectively the aldehydes that correspond to the position of the double bond are obtained, e.g. hydroformylation of trans-6-dodecene leads primarily to the formation of 2-hexylheptanal under several conditions and with several bidentate ligands. Only 1,4-bis(diphenylphosphino)butane (DPPB), which presumably acts as a monophosphine ligand,⁵⁰ yields tridecanal.⁵³ Interestingly, for the carbonylation/hydrogenation reaction of ethene oxide to 1,3-propanediol alkyldiphosphines, similar to the ligands discussed in section 2.4, provided very useful cobalt catalysts.⁵⁵

Amines, especially n-butylamine, have also been recognised as successful additives concerning rate enhancement, but product linearity decreases and high reaction pressures are still required.⁵⁶,⁵⁷ Additionally, the formation of heavy by-products significantly increases, caused by base-catalysed aldol-condensation.
In industry there is a significant interest in the development of new catalysts that are able to hydroformylate internal alkenes in a biphasic solvent system, like the Ruhrchemie/Rhône-Poulenc aqueous rhodium biphasic hydroformylation of propene. Only a few publications have appeared that address catalyst recycling via such a process for cobalt. Jenck\textsuperscript{52} and Beller \textit{et al.}\textsuperscript{58} report the hydroformylation of internal short chain alkenes using TPPTS (9) modified cobalt, from which the latter study is most detailed. Under optimised conditions regio-selectivities as high as 74\% could be obtained ($T = 130\,\degree\mathrm{C}$, $p(\mathrm{CO}/\mathrm{H}_2)(1:1) = 100\,\mathrm{bar}$, $[\mathrm{Co}] = 0.1\,\mathrm{mol}\%$). Essentially at temperatures $< 150\,\degree\mathrm{C}$ no hydrogenation takes place. Recycling experiments showed that between 0.9\% and 6\% of the total cobalt amount leached into the organic phase. The aldehyde yield even increases upon catalyst reuse, which is attributed to non-complete formation of the catalytically active species during the initial experiments. 7-tetradecene was converted with a selectivity of 77\% to $n$-pentadecanol by TPPTS/Co hydroformylation in a microemulsion obtained from surfactant Marlipal O13/80 (L/Co = 9, $T = 160\,\degree\mathrm{C}$, $p(\mathrm{CO}/\mathrm{H}_2)(1:1) = 120\,\mathrm{bar}$),\textsuperscript{59} which is a significant increase from the 34\% linearity obtained in absence of surfactant under near identical conditions (L/Co = 8, $T = 140\,\degree\mathrm{C}$, $p(\mathrm{CO}/\mathrm{H}_2)(1:2) = 130\,\mathrm{bar}$).\textsuperscript{52} The amount of alcohols produced is significantly lower than the Co-TPPP systems, but much higher than the Co-TPPTS systems reported by Beller.\textsuperscript{58} In comparison, the Rh/TPPTS emulsion systems predominantly yields 2-hexylnonanal.\textsuperscript{60,61}

![Image](image)

2.3 Platinum

Next to cobalt and rhodium, platinum is the third most widely investigated metal for hydroformylation. Most catalytic systems employing platinum are directed toward asymmetric hydroformylation, thus when internally unsatured alkenes are used the branched aldehydes are desired.\textsuperscript{62,63} One of the earliest applications of Pt-catalysts for hydroformylation of internal alkenes were reported by Schwager and Knifton\textsuperscript{64} and by Clark and Davies,\textsuperscript{65} but low yields and linearity were obtained. A more detailed study appeared from Tang and Kim for the hydroformylation of \textit{trans}-5-decene and 2-hexene using a selection of different anions, ligands, and co-catalysts under a variety of syngas pressures and syngas compositions at various temperatures.\textsuperscript{66} Marchionna \textit{et al.} corroborated their results by examining the influence of forty monodentate ligands for the hydroformylation of 2-butene and discussed them in terms of their stereoelectronic parameters ($100\,\degree < \theta < 193\,\degree$, and $0 < \chi <
Unavoidable is the lack of information on some stereoelectronic combinations, e.g. no data are available in the range $100^\circ < \theta < 130^\circ$ with $0 < \chi < 20$, and only four data points, which are in close proximity of one another, were provided in the area $\theta > 140^\circ$ with $\chi > 13$. In general, electron withdrawing ligands ($\chi \sim 30$) lead to the highest regio-selectivities, hydroformylation and hydrogenation activities, and formation of heavy end-products, thus the chemo-selectivity decreases. Systems bearing ligands with a higher $\chi$-value are unstable with respect to the reduction to metallic platinum, attributed to ligand decomposition. For both electron withdrawing and electron donating ligands the systems can be stabilised by the addition of promoters, like iminium chlorides. These systems exhibit characteristics similar to those of the cobalt systems, but under milder working conditions.

The synthesis of useful intermediates for the manufacture of nylon-6 from cheap and readily available feedstocks is an important target for industry. Hydroformylation and methoxycarbonylation are important catalytic routes toward the production of useful intermediates for nylon-6, and nylon-6, 6 from butadiene, like 3-pentenal and methyl-3-pentenoate. The hydroformylation of methyl-3-pentenoate has been widely investigated. DuPont patented platinum catalysts based on $1,1'$-bis(diphenylphosphino)ferrocene (DPPF), and derivatives of DPPF. They reported a 94% regio-selectivity toward methyl-5-formylvalerate (the linear product) ($\text{TOF} \approx 25 \text{ mol.mol}^{-1}.\text{h}^{-1}$; $p(\text{CO}/\text{H}_2)(1:1) = 68$ bar, $T = 100^\circ$) using a catalyst composition obtained from Pt(acac)$_2$/DPPF/La(OSO$_3$CF$_3$)$_3$. The use of other diphenylphosphino-bidentate ligands, like DIOP, DPPP, BINA P and DPPB, led to lower linearities and chemo-selectivities.

While trichlorostannate (SnCl$_3$) is the most widely applied catalyst promoter other promoters can also be applied. Especially various metal trifluoromethanesulfonates, lanthanide hexafluoroacetylacetonates (HFAA), tetrafluoroborates and hexafluorophosphates are suitable. The best results for the hydroformylation of methyl-3-pentenoate were obtained using La(OSO$_3$CF$_3$)$_3$, while other substrates benefit from other promoters, e.g. for trans-2-hexene better activities and regio-selectivities were obtained with Nd(HFAA)$_3$ and for trans-3-hexene slightly higher conversions were obtained by using Dy(OSO$_3$CF$_3$)$_3$. The Pt(acac)$_2$/DPPF/La(OSO$_3$CF$_3$)$_3$ catalyst system can hydroformylate several other internal alkenes, like 3-pentenenitrile, and 3-pentenoic acid, in high regio-selectivity as well.

The wide bite angle Xantphos-type ligands 10, 11, 12 and 13 were used to study the effect of bite angle on hydroformylation of methyl-3-pentenoate. (11)PtCl/SnCl$_3$ catalyst (11:Pt = 8) resulted in the most chemo-, and regio-selective Pt-catalyst reported sofar. At $80^\circ$ C only $3\%$ of hydrogenated and other by-products were formed at a regio-selectivity of $95\%$ toward the linear aldehyde. Turn-over-frequencies were low, but could be improved slightly by lowering the 11:Pt ratio to 2, albeit at the expense of regio-selectivity ($92\%$). The reaction temperature had little influence on rate of
hydroformylation, which was attributed to more formation of inactive methyl-2-pentenoate at elevated temperatures, but chemo-selectivity decreases dramatically at higher temperatures caused by a significant increase in hydrogenation activity.

Regio-, and chemo-selectivities as high as 96% at very high activities (initial TOFs ranging from 200 to 700 mol.mol\(^{-1}.h\)\(^{-1}\)) for the hydroformylation of 1-octene were obtained with 14, 15 and 16.\(^{77}\) Ligands 15 and 16 are one of the few examples where As-based ligands perform better than their respective P-ligands. For the hydroformylation of methyl-3-pentenoate Xantphos-type ligand 14 shows an activity in between 10 and 11, the high activity, however, was accompanied by a substantial amount of hydrogenation, which is also observed for 10. Linearities for methyl-3-pentenoate hydroformylation with 14 – 16 were low (2.9 < l/b < 3.7). The dramatic drop in reactivity is consistent with work of Kawabata and Hayashi and co-workers.\(^{78,79}\) It can be deduced that in the (diphosphine)Pt/SnCl\(_3\) catalysed hydroformylation the reactivity increases with increasing natural bite angle up to \(\sim 102^\circ\). Higher activities are measured for DPPF, 10 and 14, but for wider bite angle ligands, like 12, 13, 15 and 16 the activity drops. It must be noted, though, that for 10 and 14 part of the reactivity is due to increased hydrogenation activity. These results are probably caused by a shift in the rate determining step and is possibly related to different reactivity of the cis- and trans-isomers of platinum(II) complexes.\(^{77}\)

Van Leeuwen and Roobeeck obtained interesting results with diphenyl phosphinous acid PPh\(_2\)OH as ligand, since no SnCl\(_2\) or other promoter has to be added to form an active Pt-catalyst.\(^{80}\) Systems based on PPh\(_3\) and PPh\(_2\)OH led to isolable species 17\(^{81}\) that could be used as catalyst pre-cursor. This led to 70% linear product in the hydroformylation of 2-heptene, but hydrogenation was considerable yielding C\(_8\)-alcohols and heptane.

\[
\begin{array}{|c|c|c|c|c|c|}
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E/E' & X & Y & R^1 & R^2 & \beta_\text{a} (\circ) \\
\hline
10 & P/P & H,H & H,H & H & 101.6 \\
11 & P/P & SiMe\_2 & H,H & H & 106.2 \\
12 & P/P & S & H,H & Me & 106.7 \\
13 & P/P & CMe\_2 & H,H & H & 109.8 \\
14 & P/P & C\_2H\_4 & H,H & H & 102.0 \\
15 & As/As & CMe\_2 & O & t-Bu & 112.9 \\
16 & As/P & CMe\_2 & O & t-Bu & 111.4 \\
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\end{array}
\]
2.4 Palladium.

For a long time palladium was not recognised as a suitable transition metal for hydroformylation, but recently few publications using this metal appeared.82-85 In a detailed investigation by Drent and Budzelaar it is explained how delicate variations in ligand, anion and solvent in Pd-catalysed reactions can be used to steer the reaction toward alcohol/aldhyde, ketone or oligoketone formation.83 Crucial is the Pd-acyl species that can either insert an alkene to form mono-, and oligoketones (hydroacylation) or undergo hydrogenolysis to produce aldehydes (hydroformylation) (Scheme 3).

An important factor is the electrophilicity of the metal centre. If the metal centre is too electrophilic alkenes will insert in the Pd-acyl intermediate, but if the metal centre is not electrophilic enough, e.g. by applying too strongly coordinating anions, no reaction occurs. Thus, selective hydroformylation requires a moderate electrophilic Pd centre, which can be obtained by using a very basic ligand (e.g. 1,3-bis(di-sec-butylphosphino)propane) and a not too poorly coordinating anion (e.g. TFA−).

The addition of salts, like NaCl,85 can have an additional activity promoting effect, which can be further enhanced by the addition of water.84 The hydroformylation of C11/C12 alkene mixtures, isomerised to equilibrium, were converted to C12/C13 linear alcohols in 75 % using bicyclicalkylphosphines, like 18 and 19, at rates up to 200 mol.mol−1.h−1 (T = 150 °C, pCO = 40 bar).

Especially interesting is the ability to convert secondary- and tertiary alcohols to primary alcohols via a sequential condensation-isomerisation-hydroformylation-hydrogenation reaction. E.g. 3-hexanol was selectively converted to heptanol in 70% yield.82

Pd-catalysts obtained from 18 - 19 and methane sulfonic acid could be recycled at least 5 times, without showing any detectable loss of Pd, by removal of the product from the reaction mixture by distillation.85

Scheme 3 i) Hydroformylation, ii) Hydroacylation.
2.5 Rhodium.
Currently, most hydroformylation catalysts are based on rhodium. Rhodium catalysts show in general much higher activities than other metals, show a much higher regio-selectivity and do not need co-catalysts and/or promoters or have to operate under basic or acidic conditions. Thus, catalysis already takes place under very mild reaction conditions. Therefore, hydrogenation, isomerisation, and the formation of heavy end-products, are not or only in small amounts observed. Consequently, for the hydroformylation of internal alkenes the reaction conditions have to be adjusted such that the rate of isomerisation increases. Isomerisation is greatly enhanced at elevated temperatures, but the reactivity of the branched alkyl rhodium intermediate (like 4') is also considerably enhanced, thus mainly branched aldehydes will be produced. By additionally reducing the CO pressure the rate of CO-association to 4' is suppressed (less formation of 5'), and the rate of β-hydrogen elimination from 4' to form 3 is enhanced. On the other hand, 4 reverts almost quantitatively to the linear aldehyde. Thus by reducing the CO pressure and by increasing the reaction temperature catalysis is directed toward formation of the linear aldehyde.

2.5.1 Phosphines.
The rate of alkene association and CO dissociation are largely affected by the electrophilicity of the rhodium centre. Basic ligands hamper alkene coordination and CO dissociation and consequently retard the reaction, while electron deficient ligands enhance the rate of hydroformylation. Therefore, it is not surprising that most catalysts based on (triaryl)phosphine systems, like PPh₃, show poor activities and selectivities for hydroformylation of internal alkenes. Additionaly, above 145 °C PPh₃ decomposes. Trialkylphosphines, especially (bi)cyclic alkylphosphines, are thermally more stable, but product linearity is generally lower than for PPh₃. Investigations toward the effect of steric bulk (θ) on the reaction rate showed that more sterically hindered trialkylphosphines result in increased reaction rates, but reduced linearity. Although more oxygen sensitive, phosphine ligands are in general thermally and chemically more stable than more electron deficient ligands, like phosphites.
Few rhodium phosphine ligands have been reported that exhibit fast and selective hydroformylation of internal alkenes. Rhodium complexes of the Xantphos-type ligands 10, 11, 12 and 13 were reported to show preferential hydroformylation of the internal double bond during hydroformylation of methyl-3-pentenoate.\(^7\) Substitution of the diphenylphosphino-moieties for phenoxaphosphino- (20) or dibenzophosphole-moieties (21) resulted in the first rhodium diphosphine catalyst for active and highly selective hydroformylation of internally unsaturated substrates.\(^5\)\(^6\) A moderate activity, but high selectivity in the hydroformylation of \textit{trans}-2-octene and \textit{trans}-4-octene to nonanal were reported (Table 1). An inherent problem of 20 is the low solubility of the ligand, which might hamper commercial application.\(^9\) Modification of 26 by substituting \(R^1\) for neohexyl groups gave a hydroformylation catalyst for large scale operations.\(^9\) Furthermore, modification of \(R^2\) from -H to alkyl substituents usually negatively affects the activity and selectivity of hydroformylation, modification of \(R^1\) usually does not. Investigations toward the reaction rate dependence on the concentration of all reactants were explored using 26 (\(R^1 = n\)-hexyl) for the hydroformylation of 1-octene and 2-pentene. For 1-octene Type I kinetics\(^1\) can be used as starting point, but for 2-pentene a more complicated kinetic expression is required.\(^9\) A series of electronically similar wide bite angle ligands was obtained by preparing the phenoxaphosphino-analogues (the Xantphenoxaphos ligands: 22 – 29)\(^1\) of the

![Diagram](image-url)

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### Table 1 Hydroformylation using phosphacyclic diphosphines

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<th>l/b ratio</th>
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<td>trans-4-octene</td>
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$^a$Turnover-frequency = (mol aldehyde).mol Rh$^{-1}$.h$^{-1}$. $^b$R = n-hexyl.

**Scheme 3** Partitioning of the branched alkyl species 4' to 5' and 8. Compound 4 reverts almost directly to the linear aldehyde.

Xanthphos-type ligands. A clear bite angle effect on activity, selectivity and isomerisation was observed. An increase in bite angle results in lower activities, but increased isomerisation and regioselectivities. Deuterioformylation experiments proved that the intrinsic selectivity toward the linear and branched alkyl rhodium intermediate (4:4') is equal for 22, 26 and 28, while there exists large differences in regio-selectivity, which is determined by differences in rate of β-hydrogen elimination versus rate of migratory CO-insertion (Scheme 3). Additionally increased bite angles led to more isomerisation toward the internal alkene. The latter and more hampered alkene association were used to explain a decreased hydroformylation activity with increasing bite angle. Comparison of the CO-frequencies in the (diphosphine)RhH(CO)$_2$ showed that the ligands 22 – 29 are electronically very similar to their respective diphenylphosphino-analogues. This indicates that the differences in catalytic performance between the Xanthphos-, and Xanthphenoxaphos-series are most likely the result of
more effective steric bulk and increased π-conjugation, and are to a lesser extent the result of reduced phosphine-basicity.  

Currently, the highest regio-selectivities for trans-2-octene hydroformylation up to 96% were observed using dibenzophosphole ligands 30 and 31, which is attributed to a combination of a high isomerisation activity and a high preference for the formation of linear alkyl rhodium intermediates. Despite their rather low hydroformylation activity for terminal alkenes (TOF = 343 and 144 mol.mol⁻¹.h⁻¹ for 30 and 31, respectively), moderate hydroformylation activities (TOFs ~ 60 mol.mol⁻¹.h⁻¹) were observed for the hydroformylation of trans-2-octene.  

The second class of suitable bidentate phosphine ligands was developed by Beller et al. based on 2,2’-dimethyl-1,1’-binaphthyl backbone (32 - 35). Naphos already led to a moderately active, but highly regio-selective catalyst for hydroformylation of 2-pentene. The results with Naphos were improved by decreasing the phosphorus basicity of the ligand. Very high selectivities and activities were reported for the hydroformylation of various alkenes (Table 2). The results are in line with the results obtained by Casey et al., who reported the positive influence on 1/b ratios by applying electron withdrawing equatorial-equatorial chelating diphosphines, including the BISBI variant of 32. Increased activity with decreased phosphorus basicity is also commonly observed, which can be attributed to faster CO-dissociation and alkene-addition. Interestingly, hydroformylation rates of 1-pentene or 2-pentene in

![Image of ligands]

<table>
<thead>
<tr>
<th>Ligand</th>
<th>T (°C)</th>
<th>pCO/H₂</th>
<th>Ratio CO/H₂</th>
<th>Substrate</th>
<th>TOF⁻¹</th>
<th>l/b ratio</th>
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*Turnover-frequency = (mol aldehyde).(mol Rh)⁻¹.h⁻¹.*
Chapter 1

presence of 32 – 34 do not significantly differ from one another, indicating that isomerisation of 1-pentene is most likely similar in rate or faster than the hydroformylation reaction.

The relatively low regio-selectivity for 4-octene compared to 2-octene hydroformylation is attributed to slow isomerisation from 4-octene to 3-octene compared to hydroformylation from 2-octene to 1-octene, hence hydroformylation of the internal double bond occurs preferentially.

2.5.2 Phosphites.

Phosphites are very good π-acceptors resulting in facile CO-dissociation from 1 and strong alkene association to 2, additionally the rate of isomerisation is considerably enhanced compared to phosphine ligands. Strongly electron-withdrawing ligands make the metal centre more electrophilic, which might favor the formation of linear alkyl rhodium species. Therefore it is not surprising that to date the highest regio-selectivities⁹ and activities¹⁸-²⁰ reported for internal alkenes are based on (sterically hindered) (di)phosphite systems, like tri-(2-t-butyl-aryl)phosphites.²⁰ When bulky monophosphites are used for the hydroformylation of terminal alkenes often Type II kinetics is observed, but with sterically more hindered alkenes the alkene coordination is hampered, and consequently the kinetics changes to Type 1.¹⁸,¹⁰⁹ Compared to monophosphine ligands monophosphites induce a loss in selectivity, but selectivities can be improved by using diphosphite systems.¹¹⁰-¹¹³ The homogeneous nature of the catalyst requires catalyst separation by distillation, which puts thermal stress on the catalyst and can lead to deactivation. Phosphites also react more easily with the produced aldehydes, alcohols and water, which is formed when aldol-condensation takes place.¹⁹,¹¹⁴,¹¹⁵ Cyclic phosphites, however, have been reported to be very stable toward hydrolysis due to unfavourable entropy change.¹¹²

Many (di)phosphite systems known today are based on the cyclic 7-membered dibenzo[d,f][1,3,2]-dioxaphenin group 36, and often have a sterically hindered 2,2'-dihydroxy-1,1'-biphenyl backbone.⁹,²¹,¹¹⁰-¹¹³,¹¹⁶-¹²⁰ These types of ligands were first introduced by Bryant and Billig et al. at Union Carbide Corporation. Ligands 37 – 44 constitute only few examples of the ligands that were prepared over the past years and that were successfully applied in the hydroformylation of internal alkenes (Table 3).

Remarkable results were obtained by the use of Biphephos (42) for the hydroformylation of trans-4-octene to nonanal.¹¹⁷ At high rhodium concentrations (0.5 mol%), but low L:Rh ratios (6 to 10) a 95% selectivity toward the linear aldehyde was obtained in propylene carbonate, a medium-polar organic solvent that can be used in liquid-liquid biphasic reaction systems. The catalyst could be recycled at least five times. In toluene the selectivity of 75% toward nonanal is significantly lower.
Table 3 Hydroformylation using diphosphites

<table>
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"a"Turnover-frequency = (mol aldehyde).(mol Rh)⁻¹.h⁻¹.
Ligands like 42 can potentially adopt three diastereomeric forms (RRR, SRR, and SRS, with the middle descriptor used for the central bridging biphenol moiety). Interconversion of these diastereomers can occur by rotations about the biaryl axis. The different diastereomers can exhibit a different activity and regio-selectivity, which was shown by preparation of the structurally similar RRR-, and SRS-45 for the hydroformylation of propene.\textsuperscript{104} The diastereomer with the largest bite angle (SRS-45, $\beta_n = 117^\circ$) showed a much higher activity and regio-selectivity compared to the diastereomer with the smaller bite angle (RRR-45, $\beta_n = 111^\circ$). For diphosphite ligands the bite angle is probably also an important parameter as was observed for diphosphine ligands,\textsuperscript{115} since highest selectivities are achieved when either ligands with bisphenol or bisnaphtol bridges (\textit{vide infra}) are used.

DSM/Du Pont have reported 46 and various derivatives thereof that gave very high chemo-, and regio-selectivities in the hydroformylation of methyl-3-pentenoate, 3-pentenenitrile, 2-hexene and 2-buten (regio-selectivities up to 98%).\textsuperscript{9} Most likely, isomerisation is promoted by the electron withdrawing ester groups. Activities are moderate (TOF $\sim 125 - 170$ mol.mol$^{-1}$.h$^{-1}$), but no significant ligand degradation by oxidation was reported during a 250 hours continuous operation. No data was presented whether other types of ligand degradation occurred or not. Structural variants of this ligand also proved moderately to highly selective, especially 47 showed very high regio-selectivities (97%) for the hydroformylation of methyl-3-pentenoate, but this was accompanied by considerable substrate
hydrogenation (23%). Methyl-2-pentenoate is a known by-product of processes for preparing methyl-3-pentenoate and is also produced during methyl-3-pentenoate hydroformylation. α, β-Unsaturated ketones and esters are known inhibitors for hydroformylation and thus it is often required that the substrate is purified before application. In case of 46 the presence of methyl-2-pentenoate does not adversely influence catalysis, which is important when under continuous operation the unreacted substrates are recirculated to the reactor.

The hydroformylation of butadiene to 1,6-hexanediol proceeds less satisfactorily, since the main products were pentanal and 3-pentenal, only small amount of 1,6-hexanediol were formed as was also observed by others who applied various phosphines, phosphonites and phosphites for the hydroformylation of butadiene.

2.5.3 Miscellaneous.

Börner and Selent et al. introduced a new class of mono-phosphonite ligands (48 and 49) that showed very high activities, but low regio-selectivities. With 49 isomeric mixtures of octenes were hydroformylated at rates around 3000 mol.mol\(^{-1}\).h\(^{-1}\) with 48% linearity to nonanal at 140 °C under 20 bar of CO/H\(_2\) (1:1). With 48 the reaction rates are higher (approx. five-fold), but product linearity is lower (35% linearity).

The use of π-acid bidentate ligands of unsymmetrical structure 50 – 55 showed some astonishing results concerning activity for hydroformylation of isomeric mixtures of octene. Ligands 50 – 55 led to selectivities between 60 and 70% at rates varying between 3100 and 4600 mol.mol\(^{-1}\).h\(^{-1}\) at 130 °C under 20 bar of syngas.
The strong π-accepting pyrrolyl-, indolyl-, and carbozolane phosphines (56, 57, and 58 \( n = 1 - 3 \)) constitute a new class of potentially interesting ligands for hydroformylation of internal alkenes. While the initial results are far from satisfactory with regio-selectivities up to 60% at very high 56:Rh ratios (56:R = 100, \( n=3 \)), the ligands are easy to prepare and easily modifiable. The low selectivity obtained with these ligands can to a large extent be attributed to the monodentate nature of ligands 56 – 58. The bidentate ligand 59 was reported to be very active, and selective in the hydroformylation of 1-octene (TOFs up to 10,000 mol.mol\(^{-1}\).h\(^{-1}\), \( l/b > 99 \)), and shows a moderate isomerisation activity. Nevertheless, for the hydroformylation of 2-hexene TOFs of only 3 mol.mol\(^{-1}\).h\(^{-1}\) with a very low regioselectivity of 50% were measured. Possibly too low syngas pressures were applied \((p(CO/H_2)(1:1) = 5 \text{ bar})\) for this system as catalysis in presence of 56 \((n = 3)\) also showed low activities under 5 bar of CO/H\(_2\), which improved at a pressure of 10 bar of CO/H\(_2\) without losing selectivity.

A systematic investigation of the use of phosphabenzenes was recently started by Breit et al. The π-acceptor capabilities of these ligands are in between that of phosphines and phosphites. Ligand 60 was successfully employed in the hydroformylation of cis-, and trans-2-octene mixtures resulting in 24% selectivity toward nonanal with a very high initial TOF of 6933 mol.mol\(^{-1}\).h\(^{-1}\). The high catalyst activity is based on the formation of a mono-ligated metal species, which would also account for the low regio-selectivity.

2.5.4 Dual-catalytic systems.

The rate of isomerisation is definitely one of the bottle-necks in rhodium catalysed hydroformylation. Properties that are required for high isomerisation rates are directly related to rates of hydroformylation and regio-selectivity. Dividing the isomerisation and hydroformylation step between two different
catalysts could result in highly active and regio-selective conversions. In some processes the hydroformylation is preceded by a separate isomerisation step as this can be more effective than separation of isomeric alkenes by distillation, but a one-pot procedure would be easier. Only few articles have addressed this subject, the most recent and most successful was reported by Beller et al. who demonstrated the concept of a dual-catalytic process by applying Ru\(_3\)(CO)\(_3\) as the isomerisation catalyst in combination with a hydroformylation catalyst obtained from 61 and Rh(OOCCH\(_3\))\(_3\). Under typical hydroformylation conditions, but without added ligands, the Ru-catalyst shows extensive isomerisation and no hydroformylation. Ligand 61 resembles Takaya’s BINAPHOS, which has been used in asymmetric hydroformylation, and shows hardly any isomerisation and very low rates for internal alkenes. By addition of 0.5 mol% of the Ru-cocatalyst the rate of trans-2-butene hydroformylation was increased five-fold from 400 mol.mol\(^{-1}\).h\(^{-1}\) to 2000 mol.mol\(^{-1}\).h\(^{-1}\), and the regio-selectivity increased 126-fold from 1:99 to 56:44 compared to catalysis in absence of the Ru-cocatalyst. For successful application of this system the modifying ligand plays an important role, because the ligands can coordinate to the co-catalyst and inhibit isomerisation causing a decrease in regioselectivity, which was effectively demonstrated by catalysis in presence of PPh\(_3\).

3 Summary and outlook.

The hydroformylation of terminal alkenes will remain an important process, but from an economical and environmental perspective the conversion to the desired linear aldehydes from internally unsaturated compounds is preferred. Currently cobalt-based catalysts offer the best overall results; the moderate selectivities are almost independent of the amount of double bond isomerisations that have to take place, and cobalt catalysts already benefit from cheap and readily available phosphorus ligands. Hydroformylation rates are low, but cobalt is inexpensive compared to rhodium thus high concentrations can be used to obtain high space time yields.

Investigations toward new processes and technologies that eliminate the disadvantages of cobalt processes led to considerable progress in the field of rhodium catalysed hydroformylation, which
resulted in very high regio-selectivities. Nonetheless, most results are based on 2-alkenes and rates are generally too low for commercial application, while the catalyst systems that do provide high rates show a low regio-selectivity. Possibly, the key difference between the rhodium and cobalt catalysed hydroformylation is the isomerisation pathway. While for rhodium the isomerisation predominantly takes place via an associative-dissociative pathway, usually with cobalt catalysts the alkene does not dissociate from the metal prior to hydroformylation. If one can eliminate alkene dissociation from the rhodium complex, hydroformylation rates will be enhanced considerably. The new generation of modifying ligands and further insights into hydroformylation should allow the design of more efficient catalyst systems. In that respect the results obtained with the ‘new-comer’ palladium and dual-catalytic processes are very promising.

Hydroformylation is often used as starting point for many other consecutive reactions.\textsuperscript{137} The recent advances in amine synthesis via hydroaminomethylation starting from internal alkenes are very promising for the synthesis of novel functionalised secondary and tertiary amines.\textsuperscript{138} For specialty products the chemo-, and regio-selectivity are often more important than activity compared to the synthesis of bulk chemicals.\textsuperscript{139} Therefore, the results obtained with 32 already shows potential for commercial application.\textsuperscript{140}

4 Aim and outline of this thesis.

The aim of the work described in this thesis is the development of highly active, selective and sustainable rhodium diphosphine catalysts for the conversion of internal alkenes to linear aldehydes. Most of the work described in this thesis is based on recent catalyst development using phosphacyclic diphosphines as modifying ligands.

Chapter 2 describes the synthesis of a series of differently substituted Xantphenoxaphos-type ligands. The effect of aliphatic substituents on the rhodium catalysed hydroformylation and solubility in toluene was investigated. The influence of the concentration of all reactants on the hydroformylation of internal and terminal alkenes is also described.

The effect of the natural bite angle of diphosphine ligands on activity and selectivity in the rhodium catalysed hydroformylation has been studied before, but is still not completely understood. Especially concerning the hydroformylation of internal olefins few mechanistic data have been reported. The synthesis of a novel series of phenoxaphosphino-, and dibenzophosphole-Xantphos ligands that adapt a large range of wide bite angle ligands is described in Chapter 3. The effect of the natural bite angle on coordination chemistry and catalytic performance during the rhodium catalysed hydroformylation of internal and terminal alkenes using this new series was investigated and gives some additional insights
in how the bite angle affects the different reaction steps of hydroformylation. Deuterioformylation was performed to support our mechanistic investigations.

The aldehydes that are produced during hydroformylation are often not the final product. The versatile chemistry of the aldehyde group allows easy conversion of the aldehyde to e.g. alcohols and acids. Amines can also be prepared by the reaction of product aldehydes with primary or secondary amines. The new ligands, described in Chapter 3, were applied in a one-pot rhodium catalysed isomerisation-hydroformylation-amination-hydrogenation domino reaction (hydroaminomethylation) to form linear amines from internal alkenes. The performance of the ligands can to a large extent be explained by comparison with the hydroformylation results. High pressure infrared spectroscopy was used as a tool to follow hydroaminomethylation \textit{in situ} to get an impression of the different rates of each individual reaction step. This work is described in Chapter 4.

Most of the ligands described in this thesis are in general highly active and selective for hydroformylation. In order to improve the sustainability of these ligands a new easy synthesis procedure was developed that allows different modes of immobilisation to enable efficient catalyst recycling. The use of ionic liquids as liquid catalyst support is described in Chapter 5. Chapter 6 describes the use of two kinds of polysiloxane support for anchoring the homogeneous catalyst. Recycling experiments were performed in toluene and in scCO$_2$. 

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References.

1) Roelen, O. DE2,327,066, 1943.

2) Roelen, O. Ger. Pat. 849548, 1938.

3) Kurkov, V. P.; Threlkel, R. S. (to Chevron Res & Tech) US 5,196,625, 1993


14) In principle the bimolecular reaction of 6 or 6' with dihydrogen is not the only mechanism available for the hydrogenolysis reaction. There is the possibility that aldehyde formation occurs via a bimolecular elimination reaction, similar to that found for the unmodified cobalt system. See for cobalt, e.g. Azran, J. Orchin, M. Organometallics 1984, 3, 197. Heck, R. F. Organotransition Metal Chemistry, New York: Academic Publishers, 1974.


52) Jenck, J. (Fr 79 2694), 1979.


102) Xantphos type ligands bear the same ligand backbone as ligands 21-28, but are substituted with diphenylphosphine-moieties, e.g. ligands 11-13.


