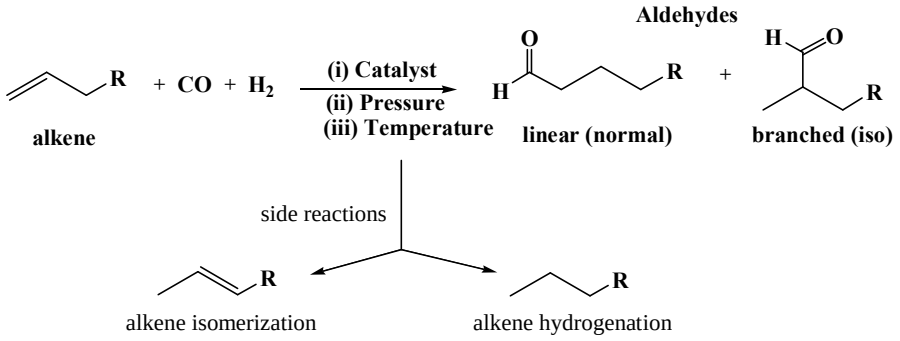
1.1. Introduction

The reaction between olefinic double bond and a mixture of carbon monoxide and hydrogen leads to linear and branched aldehydes as primary products and is known as hydroformylation reaction.



Adkins [1] has introduced the term ñhydroformylationò for this reaction, since there is attack of hydrogen and formyl group (ï CHO) at the unsaturated center of the carbon chain of alkenes. This reaction is an ideal example of atom economic C-C bond formation since the product aldehyde is formed with an additional carbon atom than starting olefin. Although the primary products of hydroformylation reactions are aldehydes, the formation of other oxygen containing by-products [2] accompanied with the side-products such as alcohols, formic acid esters, and higher boiling residues is also observed. Other products namely oxo alcohol and carboxylic acid are formed by hydrogenation and oxidation respectively of the primary oxo products, the aldehydes.

Otto Roelen discovered hydroformylation reaction in 1938 [3], during his work on increasing the chain-length of Fischer-Tropsch (FT) hydrocarbons. When a mixture of ethylene and syn-gas was passed over a fixed bed cobalt containing catalyst at 150^0C and 100 bar pressure, Roelenôs could perceive, isolate and characterize the small amount of propanal (and diethyl ketone) that had formed under the unconventional F-T conditions. It was his scientific perceptions that made him possible to link the formation of propanal from ethylene and syn-gas, which was catalyzed by metal-carbonyl formed the F-T reaction conditions. However, it took about 15-20 years for its broad applicability since the scientific community was not fully aware with the general principles homogeneous catalysis.

1.2. Economic significance of hydroformylation reaction

World production and consumption of oxo chemicals is more than 9.0 million metric tons per year. Strong market value of aldehydes and oxo alcohols are responsible for the continuous growth of the hydroformylation process. Since 1950s, the developments that provided an impetus to hydroformylation include:

- Rapid growth of the petrochemical industry
- Emergence of diverse applications of polyvinyl chloride (PVC)
- Demand of oxo products in the detergent industry

Till date, these sectors have remained the most significant users for oxo products. As a result, besides the carbonylation of methanol (to produce acetic acid) and the oxidation of *p*-xylene (to produce DMT), hydroformylation is among the most important reactions of the industrial homogenously catalyzed reactions.

2-Ethylhexanol (2-EH) and *n*- and *iso*-butanol are being produced worldwide via the hydroformylation reaction of propylene. Out of total production capacity of oxo products (Figure 1.1.), 2-EH, have the largest share, of almost 40%. *n*-Butanol, *iso*-butanol finds second and fourth position with approximately 36% and 6% respectively. Hence, on the other hand, 86% share of total production capacity is based on propylene hydroformylation or by C_4 products, which is a lower olefin. $C_{6\text{-}13}$ oxo products cover approximately a 9% share, with the balance shared by *iso*-nonanol (C_9) and *iso*-decanol (C_{10}) alcohols.

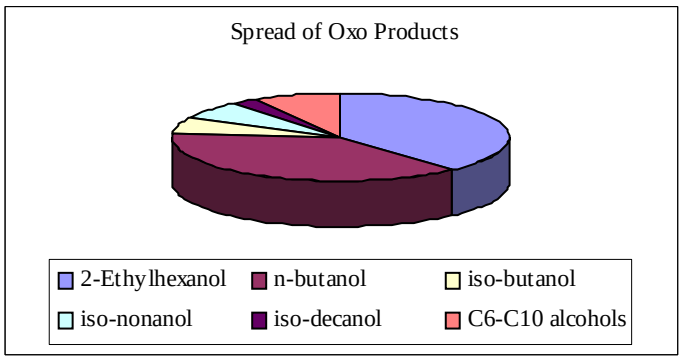


Figure 1.1. Product spread of oxo chemicals

Table 1.1. shows five-yearly-growth of oxo production in the various regions of world. The global capacity utilization fell to 79% in 2001 from 82% in 1997 because of weaker

demand and increased capacity. During the periods of 1998 and 2002, approximately 1.8 million metric tons of oxo chemical capacity was added, mainly in Southeast Asia. Therefore, data shows that Asia has been the main growth center for these chemicals during last five year while North America and Western Europe showing stagnancy. It is estimated that in the coming five years too, Asia will witness the growth (40%) in oxo products with only small increase in production capacities in other countries.

Table 1.1. Worldwide growth in the production of Oxo products (million tons/ year) [4]

Region	**1997**	**2002**	**2007**
Africa	12	333	182
Asia	1152	2071	2837
Central and Eastern Europe	358	563	525
Middle East	204	209	239
North America	1204	1382	1549
South and Central America	122	115	130
Western Europe	1662	1595	1777
World	**4715**	**5967**	**7239**

As seen from Table 1.2., Asia, North America and Western Europe contributing 32%, 23% and 31% respectively to the world production of oxo products are the major producers of today. USA and Germany with 22.9% and 21% worldôs production are the leading producers of these products in the world. Within Asia, Japan, South Korea and China are the main producers with as many as five other countries engaged in the production of oxo products. India is a minor producer contributing 0.66% to the world and 2% to the Asiaôs production of oxo products. Furthermore, it is observed from the data (Table 1.3.) that around 57% of the oxo products are produced by seven multi-national companies namely Exxon, BASF, E.ON, Dow, Celanese, Eastman and Kyowo Hakko.

Table 1.2. Region and product wise production statistics for oxo products (million tons/year) [5]

Region	2-EH	*n*-BA	*iso*-BA	*iso*-NA	*iso*-DA	C_{6-13} alcohol	TOP
Africa							198
Egypt	-	1	-	-	-	-	
South Africa	-	183	15	-	-	-	
Asia							2809
China	250	237	32	-	-	-	
India	25	15		-	20	-	
Indonesia	100	20	15	-	-	-	
Japan	365	205	57	-	150	-	
South Korea	365	30	15	-	-	-	
Malaysia	90	280	20	-	-	-	
Singapore	60	60	40	150	-	-	
Taiwan	150	60	-	-	-	-	
Central & Eastern Europe							685
Poland	170	20	20	-	-	-	
Romania	47	19	-	-	-	-	
Russia	115	196	98	-	-	-	
Middle East							218
Iran	45	12	11	-	-	-	
Saudi Arabia	150	-	-	-	-	-	
North America							2029
United States	417	1109	82	-	-	421	
South & Central America							179
Argentina	-	-	-	-	-	34	
Brazil	77	40	28	-	-	-	
Western Europe							2748
France	130	160	24	30	60	-	
Germany	740	635	54	415	-	-	
Netherlands	-	-	-	-	-	290	
Sweden	125	65	20	-	-	-	
Total World	3421	3346	531	595	230	745	8866
(%)	39	38	6	7	3	7	100

Abbreviations: 2-EH = 2-ethylhexanol, *n*-BA = *normal*-butanol, *iso*-BA = *iso*-butanol, *iso*-NA = *iso*-nonanol, *iso*-DA = *iso*-decanol, TOP = Total Oxo Production.

Table 1.3. Production of Oxo products by world-known industries (million tons/year) [5]

Industry	2-EH	*n*-BA	*iso*-BA	*iso*-NA	*iso*-DA	C_{6-13} alcohol	TOP
Celanese	300	305	39	-	-	-	644
BASF	299	584	23	75	-	-	981
LG Group	265	-	15	-	-	-	280
Eastman Chemical Company	251	247	54	-	-	-	552
E. ON	240	220	30	290	-	-	780
Mitsubishi Corporation	182	56	28	-	-	-	266
Kedzierzyn Nitrogen Works	170	-	20	-	-	-	190
Formosa Plastic Group	150	60	-	-	-	-	210
Sun Company	127	-	-	-	-	-	127
Kyowo Hakko	116	126	24	-	146	-	412
China National Petroleum	115	95	-	-	-	-	210
Interchimprom-Oxosintez	115	-	23	-	-	-	138
Hanwha Corporation	100	-	-	-	-	-	100
China Petrochemical Corporation	85	52	14	-	-	-	151
Chisso Corporation	75	-	-	-	-	-	75
Exxon Mobil Corporation	-	-	-	180	60	698	938
Dow Chemicals	-	561	42	-	-	-	603
Salavatne-fteorgsintez	-	140	42	-	-	-	182
Petronas	-	91	-	-	-	-	91
BP	-	80	-	-	-	-	80
TotalFina Elf	-	80	-	-	-	-	80
All others	867	412	92	0	0	34	1405

Abbreviations: 2-EH = 2-ethylhexanol, *n*-BA = *normal*-butanol, *iso*-BA = *iso*-butanol, *iso*-NA = *iso*-nonanol, *iso*-DA = *iso*-decanol, TOP = Total Oxo Production.

1.2.1. Oxo products: An Indian scenario

In India, the production of oxo products is limited mainly to 2-EH and *n*-butanol. Other oxo products are manufactured and consumed in small volumes. During last few years, imports of 2-EH and *n*-butanol have averaged about 10,000 to 14,000 tons/year and exports are almost negligible. In India, there are only nine major producers (Table 1.4.) of oxo products, the reason behind less production is perhaps due to sluggish growth of market for PVC plasticizers.

Table 1.4. Production of Oxo products derivatives in India (million tons/year) [5]

Industry	2-EH	*n*-BA	*iso*-BA	*iso*-DA	TOP
Andhra Petrochemicals, AP	25	5	-	-	30
Indu Nissan Oxo Chemicals, Gujarat	-	-	-	20	20
Somaiya Organics, UP		6			6
Niphad SSK, Maharastra	-	3	-	-	3
Kolhapur Sugar Mil, Maharastra	-	2	-	-	2
*Grand total**	*25*	*16*	*0*	*20*	*61*
Product spread (%)*	41	26	0	33	
Reliance Petrochemicals, Assam	50	10	5	-	65
Grand total[#]	*75*	*26*	*5*	*20*	*126*
Product spread (%)[#]	60	21	4	15	

*Data calculated up to January 2003, [#] Data calculated for 2005.

At present, Andhra Petrochemicals is a major producer of oxo products in India. Its production capacity is $30x10^3$ metric tons/year of oxo products. Out of $30x10^3$ metric tons, $25x10^3$ metric tons, 2-EH is being produced and balance is *n*-butanol produced via propylene hydroformylation reaction. In coming years, production of oxo products might have a bright future in India, if Indiaôs largest company Reliance Petrochemicals goes to produce announced oxo products with $65x10^3$ metric tons/year (Figure 1.2.). They are likely to make $50x10^3$ metric tons 2-EH, $10x10^3$ metric tons *n*-butanol and $5x10^3$ metric tons *iso*-butanol. After this much production of oxo products, India will be in position to export the oxo products, which is negligible at present.

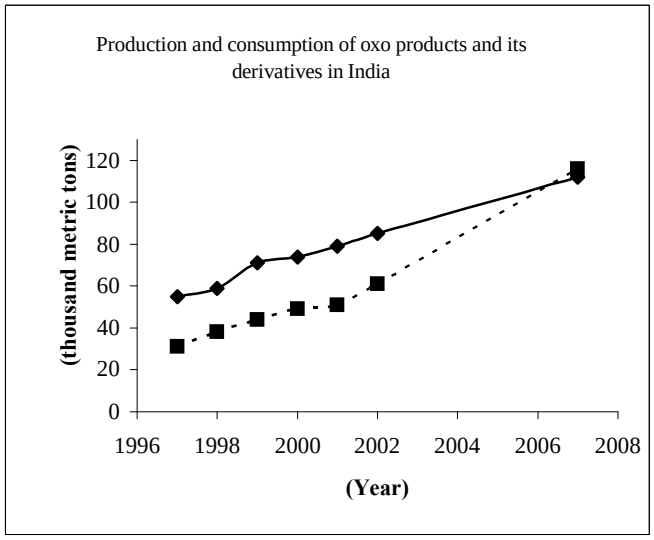


Figure 1.2. Production (dashed lines) and consumption (bold lines) of oxo products in India.

1.3. Applications of oxo products

1.3.1. Hydroformylation products of ethylene

n-Propanol and *n*-propyl acetate produced from ethylene hydroformylation account for about 70% of the U.S. propanal derivatives market. These compounds are used principally in flexographic and gravure inks, which require volatile solvents to prevent spreading and ink accumulation on printing processes. Some propanol is also converted into *n*-propylamines that are important pesticide intermediates. *n*-Propanol is also employed as a precursor for glycol ether, having primary uses in surface coating applications. The other propanal derivative, propionic acid finds application in grain and feed preservatives. Sodium and calcium propionates are used in both food and animal feed. Some propionic acid is converted into herbicides like Stam (3,4-dichloropropionanilide) and into cellulose acetate propionate, a plastic sheeting and molding precursor.

1.3.2. Hydroformylation products of Propylene

Over 90% of world consumption of *n*-butyraldehyde, which is hydroformylation product of propylene, is converted to 2-ethylhexanol (2-EH) and *n*-butanol. However, other uses of butyraldehyde are as intermediates in the production of rubber accelerators, synthetic resins, solvents and high molecular weight polymers. In total about 60% of the C_4 capacity (or about 70% of the *n*-butyraldehyde capacity) is used for producing to 2-

EH. In general, three steps involved in the production of 2-EH from *n*-butyraldehyde include aldol reaction of *n*-butyraldehyde, hydrogenation of aldol products and subsequent distillation.

2-Ethylhexanol is a valuable intermediate product for the chemical industry. Out of total production capacity of 2-EH, 34% and 25% is consumed for production of 2-ethylhexyl acrylate (2-EA) and dioctyl phthalate (DOP), these have high demand in the plastisizer industries, and remaining consumption is for different products. Some of the most important commercial relevance of 2-EH are in the synthesis of;

- phthalate plastisizers (accounting for about 72% of total global consumption) are used to plasticize the PVC. The most common is di-(2-ethylhexyl)phthalate (DOP), a general purpose plastisizer for flexible PVC. 2-Ethylhexanol is also used in the production of heavy metal salts used as PVC stabilizers.
- low volatility esters.
- 2-Ethylhexylacrylate (5.2%), which is mainly used as a monomer for acrylic resins for latex paints, especially for exterior applications.
- The derivative zincdi(2-ethylhexyl)dithiophosphate is used for lube and oil additives.

Additionally, 2-EH gives an excellent balance of adhesiveness and low emission qualities to adhesives. It also improves adhesion to a variety of substrates. 2-EH is also used as a low-volatility ingredient in solvent blends for the dyestuffs and coatings industry. It is used as a flow and gloss improver in baking finishes, as well as an additive in dispersing and wetting agents for pigment pastes. The derivatives of 2-EH are used as an additive for diesel fuel to reduce emissions. They are also used as additives to improve the performance of lube oils and mining chemicals. Miscellaneous uses, including mining chemicals, surfactants, and diesel fuel cetane improvers (2-ethylhexylnitrate).

n-Butanol is used as the intermediate for the production of butylacrylate and glycol ethers (account for 36% of total global consumption); these solvents are used heavily in the surface coating industry. Glycol ether consumption should grow in the near future as theses are used in waterborne coatings that are deemed more environmentally acceptable than coating based solely on organic solvents. *n*-Butanol is used synthesis of butylacrylate (30%), which mainly used as a monomer for the production acrylic resins

for surface coating. Much of these resins are used for outdoor latexes, where monomer imparts good durability, weathering, moisture resistant and clarity. *n*-Butanol is also used in the manufacture of herbicides, dyes, printing inks, personal care products, pharmaceuticals, plasticizers, textiles and lube additives.

1.3.3. Hydroformylation products of C_4 and higher alkenes

C_5-valeraldehyde derivatives, *n*-amyl and 2-methylbutyl alcohols are used predominantly to make zinc diamyldithiophosphate lube oil additives, which find applications in automotive anti-wear applications. Similarly, the *n*-valerate and 2-methylbutyrate esters of pentaerythitol and trimethylolpropane are used in aeromotive synlube formulation and refrigerant lubricants. C_{7-9} oxo derived acids are the principal derivatives of the C_{7-9} oxo aldehydes, are used mainly to make neopolyol esters. These synlubes are employed almost entirely in the aeromotive applications. Heptanoic acid is used to make tetraethyleneglycoldiheptanoate, which is a plastisizer. Alcohols in the C_{6-13} ranges are produced by oxo reactions and are used for both plastisizers and detergent applications. Linear C_{12-15} alcohols are used especially in detergent applications. Detergent alcohols are converted into alcohol sulfates, ethoxylates, alcohol ether sulfates and fatty amines.

1.4. Comparison of hydroformylation and non-hydroformylation route for synthesis of aldehyde/alcohol

It would be interesting to know the production of aldehydes/alcohols from non-hydroformylation (non-oxo) route have an exact idea about economically, eco-friendly nature of hydroformylation route for the production of aldehydes/alcohols.

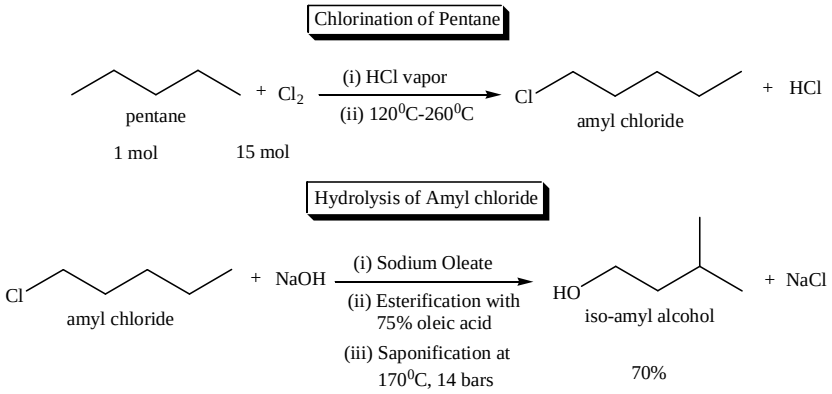
For that purpose, one can consider the production of *iso*-amyl alcohol (IAA) (IUPAC name: 3-methylbutan-1-ol) as an example. The major application of *iso*-amyl alcohol is for production of amyl nitrite (or *iso*-amyl nitrite). Amyl nitrite acts as a vasodilator (expanding blood vessels and thus lowering blood pressure) and finds applications in the treatment of heart disease such as angina. Following two commercial processes are widely used for the production of *iso*-amyl alcohol:

1.4.1. Chlorination Process

1.4.2. Oxo process

1.4.1. Chlorination process

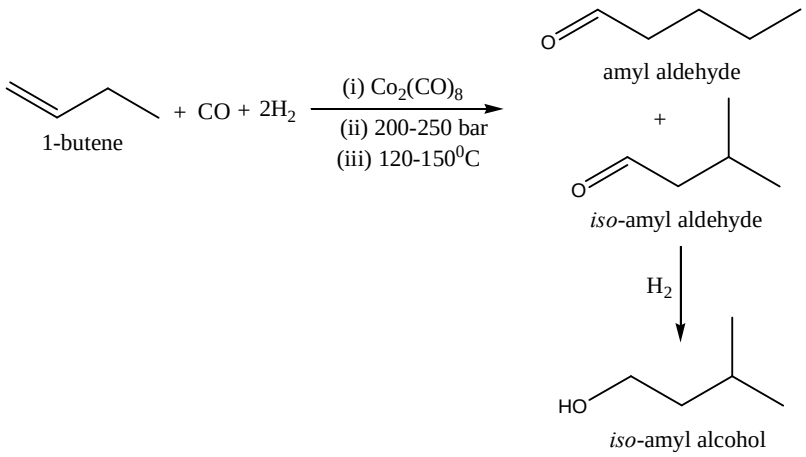
In this process, pentane is dried over HCl, vaporized, and then mixed with chlorine in 15:1 ratio. The gas enters the furnace at 120^0C, reacts and exists at 260^0C. After prompt cooling, the reaction mixture is fractionated; producing HCl and amyl chloride. Un-reacted pentanes are recycled. It is important to control the chlorine concentration and reaction severity closely to avoid the undesired dichloropentanes. The amyl chloride formed is hydrolyzed in an autoclave with aqueous caustic or sodium hydroxide in the presence of sodium oleate. Since the primary halides are difficult to hydrolyze directly, they are first esterified with 75-wt% of oleic acid, followed by saponification at 170^0C and 14 bars pressure. Final alcohol workup is via steam distillation, followed by fractionation of the isomers. The specific yield of each isomer obviously depends on the particular pentane, which is used as a feed. Overall recovery is about 70% on the initial chloride. A major problem occurs in the tube furnace, where a special alloy of iron, copper and molybdenum is needed to handle the hot corrosive hydrocarbon/chlorine/HCl mixture.



Scheme 1.1. Production route of *iso*-amyl alcohol via chlorination process

1.4.2. Oxo process

In hydroformylation (oxo) process, with the use of $Co_2(CO)_8$ cataytic system, reaction temperature in the range of 120^0-150^0C, pressure 200-250 bar and the ratio of $CO:H_2$ (1:2), more than 80% selectivity of *iso*-amyl alochol can be produced in a single step by reaction of 1-butene.



Scheme 1.2. Production route of *iso*-amyl alcohol via oxo process

Hence, the hydroformylation reaction step is rather economical because of high percentage of the total product cost associated with olefin feed. Moreover, the operating conditions can be optimized to obtain the best economic combinations of desired product yield.

The chlorination process involves the use of hazardous chlorine gas, HCl vapor, oleic acid. The disposal of effluent like HCl and NaCl is also a big problem associated with the chlorination process. Moreover, by proper optimization of catalyst and reaction conditions, the yield of *iso*-amyl alcohol can be achieved more than 80% from hydroformylation route in comparison of 70%, which is maximum yield from chlorination process. Therefore, hydroformylation reaction is a preferred route from industrial, economical and environmental viewpoint.

1.5. Catalyst developments in hydroformylation reaction

The use of catalysts is vital for hydroformylation reactions because without catalyst, this reaction is not possible or it may take longer time with an inadequate yield. Besides determining the process conditions, catalyst also control the product type and the yields obtained during hydroformylation. A general formula of hydroformylation catalysts is $[HM(CO)_xL_y]$, where M is a transition metal atom, especially platinum group metals and L is a modified ligand. These transition metal complexes interact with CO and hydrogen to form metal carbonyl hydride species, which is, generally, an active hydroformylation catalyst. Typically, complexes containing only carbonyl ligands are

known as unmodified catalysts. On the other hand, introduction of tailor-made ligand to the transition metals are known as modified catalysts.

1.5.1. Central metal atom

1.5.1.1. Monometallic catalyst systems

Among the platinum group metals, rhodium is observed to be highly active metal for hydroformylation reaction. The general accepted order of hydroformylation activity [6] for monometallic catalysts is

$$Rh >>> Co > Ru, Ir > Os > Pt > Pd > Fe > Ni$$

Relative activities, 1000 1 10^{-2} 10^{-3} 10^{-4} 10^{-6} 0 0

Presently, most of the industrial plants are running successfully with catalysts based on rhodium and cobalt complexes. However, other transition metals like Mo, Cr [7], Mn [8], Fe [9] studied largely in the laboratory are also reported to be active catalysts for hydroformylation but upto lesser extent. Ruthenium [10] is attracting the researchers for this reaction after rhodium and cobalt; nevertheless, it is yet to move from laboratory to pilot plant scale. Platinum complexes modified by $Sn^{II}Cl_2$ have gained importance in asymmetric hydroformylation. The activities and lifetime of the catalysts are the main concerns due to which the catalysts using metals other than rhodium and cobalt are not being tried in the industry. Primary work by G. Wilkinson [11] have verified that Rh/PPh_3 catalyst allowed the operation of the hydroformylation reaction at much lower pressure, which results into much lower capital and operating cost. The selectivity was also reported to be considerably higher; no hydrogenation was observed and linearity of products was as high as more than 90% in some of the reports. The projected turnover frequency (TOF) of moles product/mol of rhodium/hour is of the order of 300. Table 1.5. shows a comparative data of the cobalt and rhodium based processes.

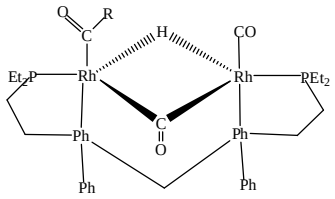
Table 1.5. Comparison between cobalt and rhodium based catalytic processes

	Cobalt		**Rhodium**	
	Unmodified	Modified	Unmodified	Modified
Active catalyst	$HCo(CO)_4$	$HCo(CO)_3(PPh_3)$	$HRh(CO)_4$	$HRh(CO)(PPh_3)_3$
Temperature (^{0}C)	150-180	160-200	100-140	60-120
Pressure (bar)	200-300	50-150	200-300	10-50
Catalyst conc. in relative to alkene (%)	0.1-1.0	0.6	10^{-4}-0.01	0.001-0.1
n/iso ratio	80:20	88:12	50:50	92:8
Amounts of by-products	High	High	Low	Low
Sensitivity to poisons	No	No	No	Yes

1.5.1.2. Polymetallic catalyst systems

Generally, bimetallic catalysts (homometallic or as clusters) show synergic effect, but progress in understanding remained slow and any advantages over conventional catalysts have not been justified based on economics [12]. Interesting results in the area of bimetallic catalyst have been reported recently [13-16], which have shown that clusters used as starting material, are degraded to at least bimetallic species, which performs the hydroformylation reaction. The most recent work of Garland [17] clearly indicates that compounds like $Rh_4(CO)_{12}$, $Rh_6(CO)_{16}$, $Rh_2(CO)_4Cl_2$, $CoRh(CO)_7$ and $Co_2Rh_2(CO)_{12}$ are degraded to the active transient species $HRh(CO)_3$ under hydroformylation conditions. The reaction is exclusively performed by monomeric Rh species. However, it cannot be excluded that under certain reaction conditions, especially at low temperature and pressures, the cluster species are more active than their monomeric counterpart [18].

High activities and selectivities in the hydroformylation of 1-hexene (n/iso = 96/4) were reported with rhodium metal with the use of the phosphine ligand $CH_2[P(Ph)CH_2CH_2PEt_2]_2$ [19]. The proposed active species **1** indicates a cooperative effect of both rhodium centers. The high rates achieved with **1**, at moderate reaction conditions, are dramatically decreased if electronically equivalent monophosphines are used instead of $CH_2[P(Ph)CH_2CH_2PEt_2]_2$. The low rates expected for electron-rich ligands were observed in this case.



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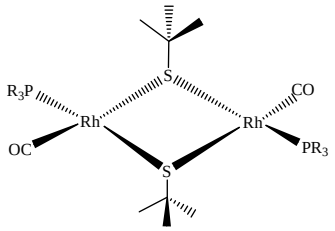
Kalck et al. [20] reported the thiolato bridged complexes $Rh_2(\mu\text{-}SR)_2(CO)_2L_2$ (**2**) (R= Bu, Ph and L = $P(OMe)_3$, $P(OPh)_3$, PPh_3) for the hydroformylation of olefin to exclusively form aldehydes in oxo-synthesis. No formation of alcohol or condensation products was observed. Compared to their monometallic derivatives, these complexes show high activities in hydroformylation of 1-hexene. A reaction mechanism has also been formulated for bimetallic systems. However, the results are similar to conventional Rh/PPh_3 systems, so that the true nature of the catalyst might be monometallic.

Similar to Kalckôs systems, fluorothiolato-[21] and aminothiolato-[22] bridged binuclear rhodium complexes [Rh (μ-SR)(L)(Lô)]$_2$ (L = Lô = COD or L = CO, Lô = PRô$_3$) have also been described as active precursors for the hydroformylation of alkenes under mild conditions (5 bar, 80^0C). Bimetallic and bi-functional as well as asymmetric variants of this basic type of catalysts have also been described [23].



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1.5.2. Ligands employed in hydroformylation catalysts

Soon after the discovery of the hydroformylation activity of $HRh(CO)(PPh_3)_3$ [11], it was found that ligands have profound influence on the activity and selectivity of hydroformylation reactions. The key to the successful growth of homogeneous hydroformylation catalysts has definitely been the exploitation of the effects that ligands exert on the properties of metal complexes. By tuning, the electronic and steric properties of a catalytically active complex, selectivities and rates have dramatically been altered.

Among the classes of compounds, which are able to coordinate to a transition metal and form complex, phosphines, are most used and accepted ligands. Nitrogen

containing ligands showed lower reaction rates than phosphine and carbon monoxide due to their stronger coordination to the metal centers. A comparative study of Ph_3R (where R = elements of Main Group V) in the hydroformylation of 1-dodecane [24] showed following order; $Ph_3P > Ph_3N > Ph_3As > Ph_3Sb > Ph_3Bi$. The majority of patents and publications in the area of hydroformylation reactions are concerned with the effect of phosphine ligands, it is therefore almost impossible to review this matter here. Instead, a study of electronic and steric effects of phosphines and phosphites and bidentate ligands would be discussed here.

Tolman introduced a concept of a cone angle θ, [25] related to steric influence of the ligands, to indicate the approximate space that a ligand occupies around the metals. It is defined by the cone, (Figure 1.3.) originating from a metal center at 2.28 Å from the phosphorus atom that confines all atoms of the substituents on that phosphorus, based on van der Waal radii. If an X-ray structure of the specific ligand is not available, this parameter can be determined via modelling of the corresponding metal-ligand fragment and then after calculation of minimized energy. For bidentate ligands, like diphosphines, Casey and Whiteker [26] developed the concept of the natural bite angle β_n as an additional characteristic (Figure 1.3.).

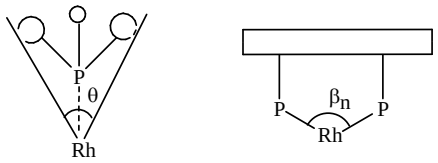


Figure 1.3. Illustration of the cone angle θ and the bite angle β_n in a rhodium complex.

The steric properties of the ligand are, however, linked with its electronic character. In the case of phosphorus ligands, the combination of ů-donation and ´-acceptor character is, therefore, to be considered. Strohmeier [27] showed that phosphorus ligands could be ranked in an electronic series based on CO stretching frequencies of the complexes. Tolman [28] expanded this work based on the carbonyl complex $Ni(CO)_3L$ for different ligands L. The electronic parameter χ is defined as the shift of the symmetric CO stretching frequency of this complex referenced to $[Ni(CO)_3(P(t\text{-}Bu)_3)]$ caused by the different bond strengths between metal and CO ligands. Phosphites are, generally, better ´-acceptors than phosphines and therefore, have great potential in hydroformylation

catalysis. This is due to presence of antibonding orbitals with ´-symmetry in the phosphite ligands. These orbitals play the role of a strong ´-acceptor on phosphorus and therefore, are competing with the coordinated CO ligands for the electron back-donation. As a result, the metal-CO bond is activated for CO dissociation, which is an essential requirement for catalyzing hydroformylation reaction and hence, rates are increased (Figure 1.4.).

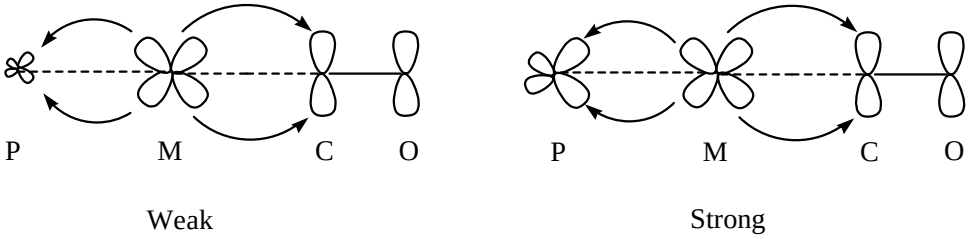


Figure 1.4. Effect on CO bonding for weak and strong back-donation towards phosphorus ligand

The use of cone angles, electronic parameters and natural bite angles has been successful for the postulation of actual catalyst system for hydroformylation reactions up to certain extent, but the prediction of exact behavior of ligands and the consequence of their applications during the course of hydroformylation reactions remain unsatisfying. The systematic studies of the influence of ligand structure on catalytic performance in the hydroformylation reaction are rare and despite the development of a wide variety of new ligands, consistent structure-activity relationship is still lacking.

1.5.2.1. Phosphines

Phosphorous ligands with low G-values such as trialkylphosphines form very stable transition metal complexes in combination with CO and therefore the activity for the hydroformylation decreases. The strong binding due to combination of donor and acceptor ligands inhibits ligand dissociation and no alkene complexation can occur. Mixed alkyl-aryl phosphines give active rhodium hydroformylation catalysts, although higher reaction temperature is required. However, In past few years the contributions of phosphines to progress in hydroformylation have been rather limited instead the major progress has been made by using phosphites of the general formula $(RO)_3P$ as ligands in rhodium-catalyzed oxo synthesis since they showed considerably high activities for the long chain olefins.

1.5.2.2. Phosphites: electronic effects

In 1987 Mitsubishi Kasei launched a 30,000 tons/year plant for the production of *iso*-nonanol by hydroformylation of octane. The catalyst was based on a rhodium-triphenylphosphine oxide (phosphites) complex, which is stabilized after the oxo reaction by addition of triphenylphosphine to avoid decomposition of during the distillation process. Therefore, after triphenylphosphine aryl phosphites were among the first ligands, which have been studied extensively for hydroformylation reactions. The results obtained with triphenylphosphine and triphenylphosphite are unusually similar at low ligand concentrations. A general trend observed (Table 1.6.) is that ligands with high G-values give a higher selectivity towards linear products. The trend towards higher linearities breaks down at two instances; one involves rather bulky ligand with a Ū-value of 190^0, the other one involves hexafluroisopropyl phosphite having a very high G-value. Both give rise to unstable rhodium carbonyl complexes either due to steric or for electronic reasons. The G-value of the hexafluroisopropyl phosphite ligand of 51 is very high indeed and shows (Table 1.6.) that electronically it is very similar to CO, i.e., a strong electron acceptor. Hence, the susceptibility of its mixed carbonyl hydride rhodium complexes to lose CO is similar to rather unstable $HRh(CO)_4$.

Table 1.6. Hydroformylation with rhodium phosphite and phosphine catalysts

Ligand PR_3, R =	G-Value	Ū-Value	Linearity of product
n-Bu	4	132	71
n-BuO	20	109	81
Ph	13	145	82
PhO	29	128	86
2,6-$Me_2C_6H_3O$	28	190	47
4-ClC_6H_4O	33	128	93
CF_3CH_2O	39	115	96
$(CF_3)_2HCO$	51	135	55

Reaction conditions: 90^0C, 7 bar, 1-hepetene, ligand/rhodium varied from 3:1 to 20:1

1.5.2.3. Phosphites: steric effects

Highly bulky phosphite ligands (like Figure 1.5.) yield an unstable rhodium complex. The cone angle of the ligands shown to be as high as 175^0 and the complex formed with rhodium has the formula $HRh(CO)_3L$. Apparently, not enough space remains for the coordination of second phosphite group. In a trigonal bipyramidal complex, there is no room for two bulky ligands at the two axial positions and this would leave an equatorial position for a ů-bonded hydride, which is energetically unfavorable. The mono-ligand complexes cannot be isolated and has only been observed under a pressure of CO and H_2 [29]. This complex easily loses CO, which enables coordination of a molecule of incoming alkene during the course of the hydroformylation reactions. Additionally, due to very rapid consumption of CO the mass transport of CO can become rate determining, which results in highly unsaturated rhodium complexes giving a rapid formation of terminal to internal alkenes. In the extreme situation, this means that it makes no difference whether we start with terminal or internal alkenes. As a result, complexes with bulky phosphite ligands are very reactive towards otherwise unreactive substrates such as internal alkene like 2,2-dialkyl-1-alkenes. The rate of reaction reaches the same values as those found with triphenylphosphine, upto 15,000 mol of product per mole of rhodium complex per hour at 90^0C and 10-30 bar.

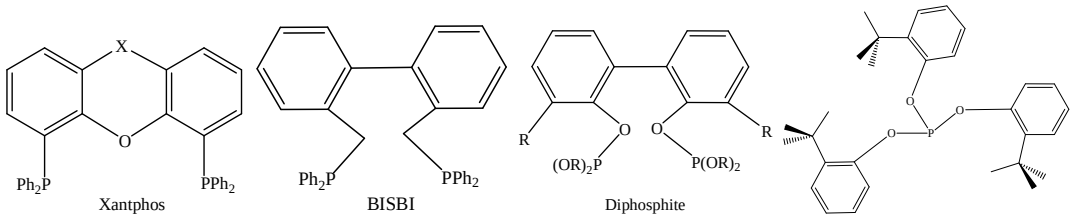
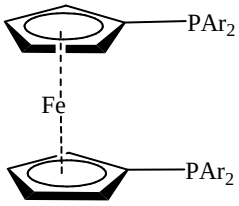


Figure 1.5. Series of bidentate ligands and 2-*t*-Butylphenylphosphite, convenient bulky phosphite ligands

When terminal alkenes are subjected to hydroformylation with these monodentate bulky phosphite catalysts, an extremely rapid hydroformylation takes place with turn over frequencies up to 160,000 mole of product per mole of rhodium per hour [30]. A moderate linearity of 65% can be achieved. Since hydroformylation of internal alkenes is also relatively fast with this catalyst, the overall linearity obtained may become rather low (20-30%). This explains the low linearity quoted in Table 1.6. for 2,6-dimethylphenylphosphite.

1.5.2.4. Diphosphines: electronic effects

Unruh, Casey and Leeuwen [31-33] have reported the electronic effects of diphosphine ligands. Unruh have studied the hydroformylation of 1-hexene using substituted ferrocene derived diphosphines $Fe(C_5H_4PR_2)_2$ **3**.



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The electronic influence of the substituted aryl groups, Ar, follows a similar trend as that observed for phosphites; higher G-values lead to higher linearities (Table 1.7.). Interestingly, the author also reported the rates and selectivities for the isomerization, side reaction to 2-hexene. It turns out that under the conditions employed; only a slight increase to isomerized alkene occurs. The rate of hydroformylation increases with increasing ´-acceptor capability of the ligand. The study clearly showed that the selectivity to linear product accurately increases with increasing G-values.

Table 1.7. Hydroformylation with substituted ferrocene based aryl diphosphine (Figure 1.5.)

Ar	3.G_i-Value (Ar)	Linearity (%)	Relative rate	Isomerization 2-hexene (%)
Ph	4.3	81	7.2	4
p-Cl-C_6H_4	5.6	87	9.3	5
m-C_6H_4	6.0	89	13.7	5
p-CF_3-C_6H_4	6.8	92	13.8	6

Reaction conditions: 110^0C, 8 bar, 1-hexene, χ_i is defined as the χ-parameter for one constituent in the equation $\chi = \times \chi_i$ for $(R_i)_3P$.

The effects could be explained along two lines and in the absence of complete kinetic data; discrimination between the two was not easy. Firstly, there may be a direct electronic preference for the formation of a higher proportion of the linear alky intermediate when the ´-back-donation to the phosphine ligand increases. The effectiveness also depends on the kinetics of the catalytic process. Alternatively, but with similar kinetic limits, the effects of χ-value may be indirect. On the other hand, it is known that a more crowded complex will favor a linear alkyl intermediate, which leads to linear aldehydes due to steric reasons. Complexes of aryl phosphine ligands with higher G-values are more stable, leading to the formation of more crowded complexes. If steric effects are dominant, one would expect at least a slight decrease of the reaction rate with increasing G-value and linearity of the products. This certainly holds for triphenylphosphine-modified catalysts. Since this is not the case here, it is tempting to accept a ódirectô electronic effect on the linearity, be it kinetic in origin (alkene insertion) or thermodynamic (*n*-alkyl-metal v/s *i*-alkyl metal stability).

Based on above discussions, the following conclusions for the higher selectivity of phosphine and related ligands can be drawn for the formation of straight chain products:

1. Combination of the electronic and steric effects of σ-donating and bulky ligands PR_3 on the migration route of hydride ligand to the alkene (both effects favor anti-Markownikov addition of hydrocarbonyl metal complex to alkene)

2. Steric effects of PR_3 ligands on the transition state of the CO insertion step (a higher rate constant of CO insertion into *n*-alkyl-metal carbonyl over that into *iso*-alkyl-metal complexes).

1.6. Characterization of intermediates in hydroformylation reactions

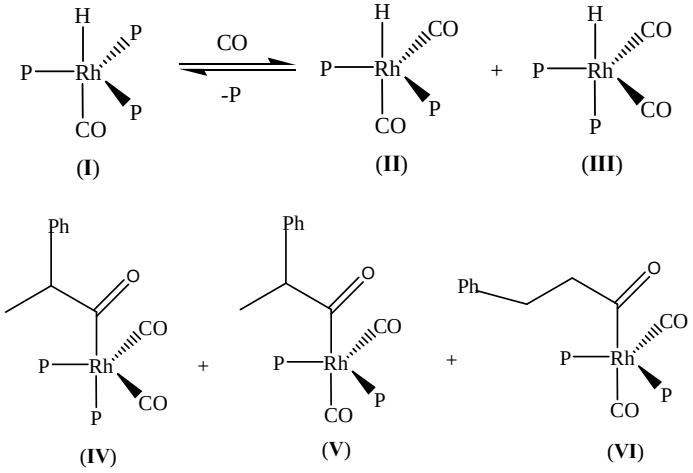
The intermediates, which play vital role in a cycle of a homogeneous hydroformylation catalyst, can be characterized by various spectroscopic techniques such as NMR, IR, Raman spectroscopy, UV-Vis spectroscopy. If an intermediate crystallizes from a reaction mixture, the structure can be solved with single crystal X-ray analysis. However, only on rare occasions do intermediates crystallize from the reacting systems since their concentration are low and hence, one turns to model compounds of the actual catalyst by changing the ligand or the metal. For example, iridium complexes show same catalytic behavior as the rhodium complexes. Since they are often very lethargic complexes than the rhodium complexes, therefore, the intermediate of iridium complexes can be captured. Another common approach is the synthesis of a ligand that simultaneously contains the substrate of the catalytic reaction; this may also lead to the isolation of likely intermediates.

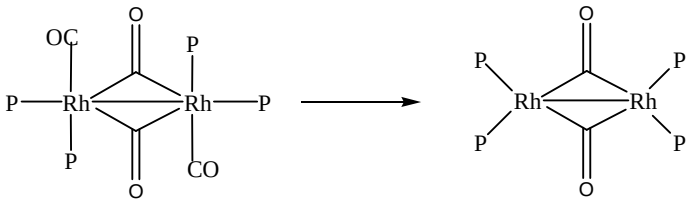
1.6.1. NMR measurements

As many of the nuclei of the hydroformylation catalysts (^{1}H, ^{13}C, ^{31}P, ^{103}Rh and ^{107}Pt) are amenable to NMR studies, therefore NMR is particularly useful technique to have information on the structure of the hydroformylation complex catalysts and the actual intermediates.

The hydride precursor of the hydroformylation catalyst has a trigonal bipyramidal structure in which the two phosphorous ligands can occupy either two equatorial sites or one axial and one equatorial site. Recently, [34-38], many hydroformylation catalyst precursors and intermediates have been identified by NMR spectroscopy. Especially those containing bidentate ligands can be easily analyzed. The coupling constant of hydrogen to phosphorous is very small when these are in *cis* position. The values of 10 Hz are often indicative of fast exchange between isomers containing equatorial and apical ligands. Coupling constant of phosphorous-phosphorous are very large for two ligands in equatorial positions, but small for ligands in *cis* orientation.

Brown and Kent [39] studied the species involved in the hydroformylation of styrene and 1-dacene with the catalyst precursor $HRh(CO)(PPh_3)_3$ at ambient pressure and temperature of -80^0 to $+25^0$C. The authors have intentionally used high catalyst concentration upto 0.02 mol/l, which is considerably higher than the concentration used in typical catalytic experiments (<0.5 mmol/l) because the conventional catalyst concentration ranges used in hydroformylation reactions are inadequate for NMR concentration ranges. They observed that under an atmosphere of syn-gas, $HRh(CO)(PPh_3)_3$ (I) transforms to $HRh(CO)_2(PPh_3)_2$ (II) and (III) and free PPh_3 (Scheme 1.3.). At room temperature, a rapid exchange with free phosphine and CO was observed. Two isomers for $HRh(CO)_2(PPh_3)_2$ (II) are observed (Scheme 1.3.): isomer (II) has two equatorial phosphines, the isomer (III) has one equatorial and one axial phosphine, and the isomer (II) was the dominant species. When $HRh(CO)_2(PPh_3)_2$ (II) reacts with styrene, the branched acyl complexes (IV) and (V) are formed and the isomer (V) was the major species (Scheme 1.3.). This was presumably due to steric factors. The branched isomers slowly isomerize to the linear acyl complex (VI). This shows that at low temperature, the kinetic product in the first reaction with styrene is branched styryl intermediate. With 1-decene, only the linear acyl complex is observed. Interestingly, a fast intramolecular exchange of the two distinct phosphines in the complex has been observed. At higher temperatures, a rapid exchange with free CO and PPh_3 was also found. Formation of dimeric species (VII) and (IIX) is a general feature of these studies.

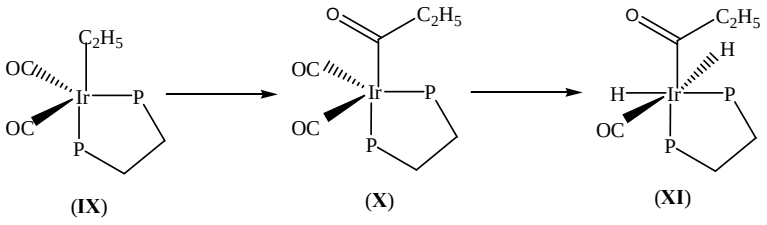




(**VII**) (**IIX**)

Scheme 1.3. Rhodium complexes found by NMR during hydroformylation of styrene (P = PPh_3)

The reaction with dihydrogen could not be tracked down in this study. Iridium forms much more stable complexes than rhodium and therefore it has been studied to obtain more details about the actual intermediate complexes and the mechanism of rhodium hydroformylation. Using an iridium complex, Eisenberg et al. [40] succeeded in the identification by NMR of all species involved in the catalytic cycle (Scheme 1.4.); the ethyl complex (IX) the propionyl complex (X) (including X-ray structure determination), and moreover, the dihydride adduct (XI). The latter gives the aldehyde product upon decomposition. These series of complexes and their reactions suggests that in the case of iridium the last step in the hydroformylation involves an oxidative addition of dihydrogen. This is the first direct proof of such a mechanism. However, it not necessarily true, for the Rh/PPh_3 modified catalyst, let alone all rhodium catalyst. For instance [39], when the acyl complexes mentioned above were done at high temperature, aldehyde was formed even in absence of dihydrogen, which would support a bimetallic step for the product information.



(**IX**) (**X**) (**XI**)

Scheme 1.4. Iridium complexes showing stepwise hydroformylation

However, the characterization of hydroformylation catalyst intermediates with NMR techniques, have two general limitations.

1. The concentration region that can be studied by NMR (10-100mmol/l) is well above the region of the active hydroformylation catalysts (<1mmol/l). Metal-ligand equilibria may shift considerably with concentration, which makes a direct

comparison of NMR data and catalytic cycles unrealistic. The reaction may become too fast at the high concentration used for NMR; too fast for *in-situ* study.

2. When the gases are getting consumed during the course of hydroformylation reaction, it is almost impossible to run *in-situ* spectra; high pressure NMR tubes allows the study of complexes under pressure, but when gas is consumed the pressure will drop quickly (high catalyst concentration) and mass transfer may also be a limiting factor in the absence of stirring.

1.6.2. IR measurements

The i*n-situ* IR measurements overcome the problems mentioned in *in-situ* NMR spectroscopy. However, the information that we obtain from vibrational spectroscopy is of lesser detail than that from NMR. The triphenylphosphine modified rhodium hydroformylation catalyst could be studied *in-situ* with IR under a variety of reaction conditions. As far as high-pressure spectra are concerned, they usually measured in the cells that are connected via a pump with the autoclave in which the reaction is taking place. This disadvantage is that mass transport limitations of the reacting gas and temperature variations may strongly influence the results. To circumvent these problems, Moser introduced a new type of cell, which utilizes cylindrical internal reflection (CIR) through a transmitting crystal that is mounted in the autoclave, submersed in the liquid phase where the reactions are taking place. The signal-to-noise ratio of the CIR-FTIR cells is less than that of common transmission cell.

Moser studied [41] the in-situ IR spectra of the $HRh(CO)_2(PPh_3)_2$ complex catalysts at 70^0C and pressures of 11-34 bar. Under a pressure of syn-gas or presence of an excess phosphine the species present were observed to have the formula $HRh(CO)_2(PPh_3)_2$. In the presence of 1-hexene the main species observed is still hydride $HRh(CO)_2(PPh_3)_2$. The absorptions of a minor species are assigned to the corresponding alkyl rhodium complex $Rh(C_6H_{13})(PPh_3)_2(CO)_2$. This observation is consistent with a slow dissociation of a ligand from the starting hydride, dependence on CO or PPh_3 (or both) and proportional relation of the rate with the alkene concentration. Another observation worth mentioning is the formation of the dimers (VII) (Scheme 1.3.) under hydroformylation conditions, especially when the rhodium concentration is high, hydrogen pressure and the temperature are low [42]. The presence of the orange dimer under reaction condition is

important, because it explains why in many cases, the rate of reaction increases when hydrogen pressure is raised. Hence, due to various advantages of IR spectroscopy, the study of hydroformylation catalyst species with the aid of IR has now become subject of meticulous reviews [33-34].

1.7. Recent trends in hydroformylation catalysis

Despite of many advantages of homogeneous catalytic systems from activity and selectivity viewpoint over heterogeneous catalytic systems, many homogenous catalytic systems have not been commercialized because of one major disadvantage compared with heterogeneous catalysts: the difficulty encountered when trying to separate the reaction product from the catalyst and from any reaction solvent. This problem arises because the most commonly used separation method, distillation, requires elevated temperatures unless the product is very volatile. Most homogenous catalysts are thermally sensitive, usually decomposing below 150^0C. The thermal stress caused by product distillation even at reduced pressure will, therefore, often decompose the expensive catalyst. Other conventional processes such as chromatography or extraction also lead to catalyst loss. The homogeneous catalysts, which have been commercialized so far, either involve volatile substrates and products or do not contain thermally sensitive ligands. As for as hydroformylation reactions is concerned, rhodium catalysts typically work under mild conditions (100^0C, 25 bar), giving good activity and selectivity (80 to 90%) to the desired linear aldehyde. Nonetheless, majority of the oxo plants use cobalt catalysts, which require much harsher conditions (typically 200^0C, 100 bar) and give poorer selectivities for linear aldehyde, because rhodium catalysts decomposes when attempting to distill the product from them. In addition to that, cobalt catalytic system can be recycled after distillation of products by the industrially well-known procedure called as ñdecoblatingò. Solving the product separation problem for the rhodium catalyzed hydroformylation reaction in an effective and economically robust way would represent a major step forward in homogeneous catalysis.

The new processes under investigation for hydroformylation reaction can broadly be grouped into two types. In the first, the catalyst is anchored to some kind of soluble or insoluble support, and the separation is carried out by filtration technique. This type of process is often referred to as heterogenizaton homogeneous catalysts. The other type

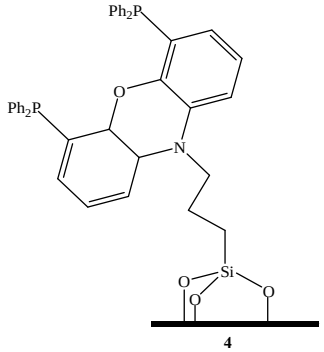
involves designing the catalyst so that it is solublized in a solvent that, under some conditions, is immiscible with the reaction product. These reaction involve two phase and are often referred to as biphasic systems. A variety of systems have been designed will be discussed in following sections.

1.7.1. Supported catalysts and filtration

1.7.1.1. Insoluble supports

Ligands can be anchored onto solid materials such as inorganic oxides (often silica) or polymers. If the anchoring is covalent, it can be strong enough to withstand the rather harsh conditions of the catalytic reaction. Because the ligand for binding the metal exists in only on accessible sites of the solid and can be designated to extend beyond into the solvent, all catalytic active sites are available for reaction, allowing rates and selectivities comparable to those obtained with analogous dissolved catalyst. The main problem, however, is that bonds between metals and ligand are often broken and reformed during the course of catalytic reactions. If this happens, the catalyst may break away from the support and becomes dissolved. This ñleachingò process leads to loss of activity of the catalyst when it is recovered by filtration and recycled, or is used with a continuous flow. The leaching problems have been overcome upto certain extent when the catalyst was anchored inside the pores of zeolites (so-called ship-in-a-bottle catalysts) or of mesoporous solids.

Recently, a system for hydroformylation reactions was reported in which a member of highly selective Xantphos family of ligand was derivatized with a hydrocarbon chain terminating in a triethoxysilyl group [43-44]. This ligand was incorporated into a sol-gel solution for the production of silica and the resulting supported ligand, **4** bound to rhodium.



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This catalyst shows high activity and selectivity, and a single sample has been used for a variety of different hydroformylation reactions under widely varying conditions over a period of more than a year. The catalyst still retains its activity and selectivity, providing a very rare example of where leaching has been reduced to an acceptable level [44-45].

Since the lower alkenes exist in gaseous form, practically it seems appropriate to produce aldehydes and related products under continuous flow conditions over conventional metal catalysts. In hydroformylation, the rate and selectivity are dependent on the metal applied (Table 1.8.). Rhodium catalysts are the most selective towards oxo products, while Pd reveals the highest activity, even at low temperature (but selectivity is low). Thus, there is an obvious correlation between the ability of a metal to catalyze the formation of aldehydes from alkenes and syn-gas.

Table 1.8. Propylene hydroformylation over various SiO_2-supported metal catalysts[a] [46]

Catalyst	Temp. (K)	TOF[b] x 10^6 (s^{-1})		Selectivity (%)	
		HF[c]	Propane	Aldehyde	*n*-isomers
Rh	388	2.1	3.8	66	74
Pd	300	2.2	130	62	22
Pt	453	15	510	39	53
Ni	453	1.5	330	10	89
Ru [f]	453	36	432	68	87

Reaction conditions: [a]At 23.3 kPa of H_2:CO:C_3H_6 = 4:2:1 mixture, [b] Turnover frequency (the reaction rate per surface metal atom), [c] HF = Hydroformylation.

The hydroformylation with the metals incorporated into the zeolites X, Y and A [47-50] and layered silicate clay such as smectite, hectorite [51] as a catalyst is quite conceptual due to following two reasons:

(i) they can easily be exchanged with cationic metal such as rhodium and/or cobalt,

(ii) the zeolite lattice as well as restricted interlayer region of clays may allow the passage of normal isomer and inhibit the passage of branched isomer and thus may promote regioselectivity.

Catalytic activities and selectivities achieved in the gas phase hydroformylation of alkenes over supported metal catalysts can be markedly influenced by other variables

including supports and promoters. As a function of support, the hydroformylation activities of Rh catalyst prepared by thermal decomposition of $Rh_6(CO)_{16}$ follow roughly the order of support: ZnO>MgO>TiO_2, ZrO_2, La_2O_3>>>SiO_2, Al_2O_3 [52]. This proves the validity of alkene hydroformylation as a model test reaction in order to elucidate whether the promoters influences the CO insertion step of oxygenate formation from syn-gas.

Modification of Rh/SiO_2(ZrO_2) catalysts by adsorbed sulfur [53] or particularly, selenium [54] offers a noteworthy boost in the oxo selectivity (up to four times that of un-promoted Rh/SiO_2). Atoms of sulfur and selenium block preferably the sites for H_2 dissociation on the rhodium metal surface and suppress the alkene hydrogenation. The addition of Zn^{2+} or Fe^{3+} to Rh/SiO_2 results in a similar dramatic enhancement of the oxo selectivity [55]. Due to their Lewis acidity, these promoters can behave as electron acceptors activating Rh-bonded carbonyl ligand for nucleophilic attack of alkyls and stabilizing the acyl species.

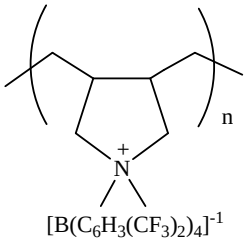
In the presence of some other Lewis acids such as TiO_x, MnO_x, ZrO_x and NbO_x [56], electropositive additives alkali earth metal oxides [57] or (Na^+) [58], increases the rate constant of CO insertion step in the oxo reaction on Co, Rh, or Pd catalyst, although, changes in the oxo selectivity are not so significant since these promoters stimulate and enhancement of hydrogenation abilities of Group VIII metals. It seems that, a procedure used to introduce a promoter should provide the close atomic level contact between the promoter and catalytically active sites. In conclusion, metal catalysts for hydroformylation, because of their low activities and low oxo selectivities, are yet unfavorable compared with metal complex systems.

Recently, Chaudhari et. al. [59] demonstrated the heterogenization of $HRh(CO)(PPh_3)_3$ to zeolite-Y support via tethering through phosphotungstic acid. This novel hydroformylation catalyst showed excellent stability, reusability and even improved activity. The activity, selectivity and stability of this catalyst for hydroformylation of a variety of linear and branched olefinic substrates have been confirmed. The heterogenized catalyst was recycled several times without the loss of any activity.

1.7.1.2. Soluble supports

The supports used to bind the catalyst may be soluble in the reaction medium. This has the advantage that active catalytic sites are dispersed throughout the reaction

solution. The catalyst architecture can be similar to that of the efficient homogenous catalyst. The supports may be soluble polymers [60-61]. In a recent example, the anions of **5** were partially exchanged by anions of **6** (n = 0). The resulting polyelectrolyte was used to catalyze the hydroformylation of 1-octene, with catalyst product separation being performed by ultrafiltration. Approximately, 93% of the catalyst could be recycled with high turn-over-frequency (TOF) and the losses of catalysts were attributed to ligand oxidation during the many manipulations required for batch process.



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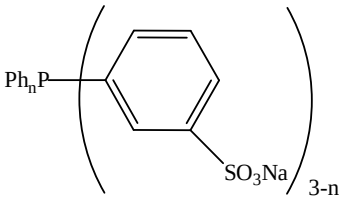

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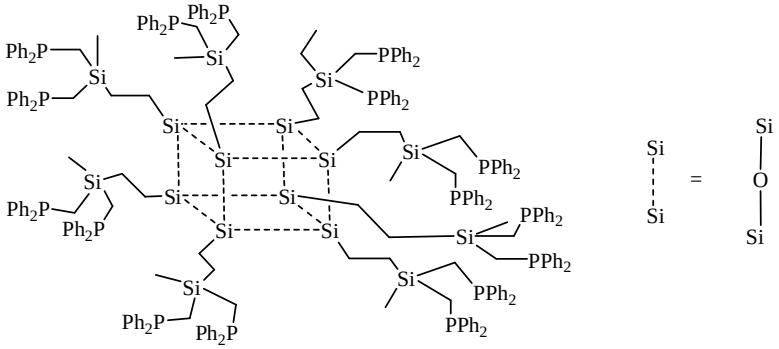
Dendrimers are large (2 to 4 nm) tree-like molecules with a persistent globular shape, which makes them more suitable for ultrafiltration than soluble polymers, which may pass through filtration membranes more easily. The identical groups on the periphery of the dendrimer can form complexes. The metal-binding groups are usually on the exteriors of the dendrimer but can also be buried within shape-selective pockets. Because membranes for enzyme ultrafiltration have channel ~ 1 nm in diameter, they allow the solvent and products of a catalytic reaction to pass but reject the dendrimer-based catalyst. Advantageously, dendrimers may exhibit bidentate binding (through two donor atoms on the same dendrimer arm) to the metal. The chelate (ring-forming) effect will then ensure that leaching is minimized. Furthermore, if the metal separates from its dendrimer-bound ligand, it may be sequestered again rapidly by one of the many identical binding sites nearby. Despite these advantages, reaction where ultrafiltration has been attempted has generally shown loss of activity upon recycling [62]. This may not be because of genuine leaching, but because the membranes are not designed for use with organic solvents, high temperatures and/or high pressures. One rather unexpected advantage of some dendrimers has emerged, however; they can show much higher selectivities to desired products than small-molecule analogs. For example, a dendrimers bearing 16 PPh_2 groups on its periphery, **7** gives linear: branched (l:b) ratios in the

hydroformylation of 1-octene of 13.9:1, compared with 3.8:1 for small molecule analog [63].



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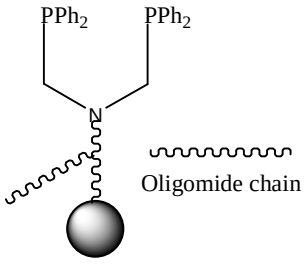
In a recent study, dendrimer wedges (molecules that have dendrimer like properties but only form part of a sphere) were anchored to beads of silica [64] or a polymer, **8**, using approaches developed for solid phase organic synthesis. They have been used for hydroformylation and can easily be removed by conventional filtration. This procedure combines the advantages of the controlled environment of the dendrimer-bound catalyst with the ease of separation of the supported catalyst. In this application, the metal-binding phosphine groups may be placed to the end of or along the arms of the dendrimer. Both types of binding allow high catalytic activities for the hydroformylation of styrene and related substrates, but dendrimers in which, the rhodium is more deeply buried show better recyclability [65].



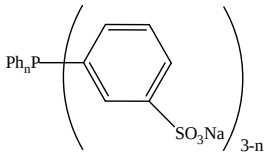
8

1.7.2. Biphasic systems

1.7.2.1. Aqueous biphasic system

A major advancement in the catalyst recovery in recent years has been the introduction of water-soluble phosphine which is referred as biphasic system that has been commercialized for the hydroformylation of propylene uses as a ligand a sodium

salt of sulfonated triphenylphosphine (TPPTS) (**9**, n = 0) [66] to make the rhodium based catalyst soluble in water. Because most organic compounds do not mix with water, the reaction can be carried out in two phases with rapid mixing to ensure maximum contact between the catalyst and the substrate. After the reaction, the product is decanted, leaving the catalyst in aqueous phase.



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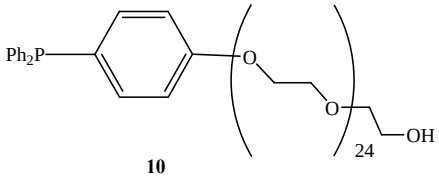
There is pH dependant equilibrium between the water-soluble and organic soluble forms of TPPTS. The protonated form is extractable with organic solvent between the pH 0 to -1 while at higher pH the sodium salt is water-soluble to the extent of 1100 g/l. The non-toxicity of the TPPTS ligand (an oral LD_{50} = 5g/kg) is another feature that makes large-scale industrial application possible.

Hydroformylation of propylene is successfully being carried out water-soluble catalyst systems. The solubility of propylene in water is sufficiently high to give an acceptable rate of reaction. The use of buffer component such as Na_2HPO_4, has been suggested for control of pH. However, the use of such salts has been shown to have definite influence on the reaction rate as well as product selectivity. The high efficiency of the recovery process ensures that rhodium losses are in parts per billions (ppb) ranges. Ruhrchemie/Rhone-Poulenc (RCH/RP) reports that over a period of 10 years, for the production of 2 million tons of *n*-butyraldehyde, the loss of rhodium has been approximately 2 kg only.

However, one of the problems with the use of water-soluble catalysts is the poor solubility of other higher alkenes in water, which led to low reaction rates and hence, the process of aqueous-biphasic system is limited to short chain alkenes. Another drawback is that the water itself is highly protic coordinating molecule that has tendency to interact with organometallic complexes used for hydroformylation reaction. A recently reported approach solves this problem while retaining the advantages of aqueous biphasic systems [67]. Instead of being sulfonated, triphenylphosphine was derivatized with a polyethylene glycol chain (**10**).



10

At room temperature, the rhodium complex of **10** is water-soluble and insoluble organic solvents. Upon heating, however, the polyether side chains undergo a phase transition and the complex becomes more soluble in organic phase than in water, so that at reaction temperature all the required components are dissolved in the organic phase. Upon cooling, the phase transition is reversed and returns to the aqueous phase, now devoid of rhodium complex, can be decanted.

Since the entire biphasic, catalysis relies on the transfer of organic substrates into the aqueous phase containing the catalyst or at the interphase. Therefore, the researchers have paid attention on improving the affinities between these two phases. The addition of co-solvents [68], surfactants [69] and modified cyclodextrins [70], to enhance the mutual solubility of the components across the phase periphery can boost the reaction rate potentially. The use of micellar systems in hydroformylation reaction has been reported [71] to overcome the problem of solubility of substrates up to some extent. The combination of hydrophobic and hydrophilic properties within one molecule presents unique properties to amphiphilies upon dissolution in water. At very low concentrations, these amphiphilies behave as normal electrolytes but if their concentration is increased above the so-called critical micellar concentration (CMC), they have ability to aggregate under reaction conditions and could improve the solubility of the substrates. The basic idea is to add an appropriate amphiphilic agent (surfactant or detergent) to the biphasic liquid system, so that the aqueous and organic phases form a single stable micellar medium or a micoemulsion, with continuous and dispersed phase. Micelles can dissolve molecules, which are normally not soluble in common solvents. Moreover, due to the very small size of micelles (10-100nm), there is an enormous increase of the interface between the continuous and dispersed phases. There are reports [72] that enlighten that TPPTS ligand showed higher activity towards hydroformylation of higher olefins in the presence of cetyltrimethylammonium bromide (CTAB). Effect of different surfactants for the hydroformylation of 1-dodecene is well documented by Li et al. [72]. They observed

that addition of cationic surfactants enhanced dramatically the reaction rate. Addition of nonionic surfactants did not enhance the rate of 1-dodecene hydroformylation and the anionic surfactants inhibited the reaction. The rate of hydroformylation of 1-dodecene increased with increasing stirring rate, but the normal/iso ratio of aldehydes decreased supporting the fact that the micelle structure creates an orderly and compact micro circumstance where alkene was solubilized and coordinated with metal complexes, which, was favorable for the formation of linear aldehydes. The vigorous stirring conditions disturb the meta-stable micelle structure and hence, decrease in selectivity of *n*-aldehydes was observed.

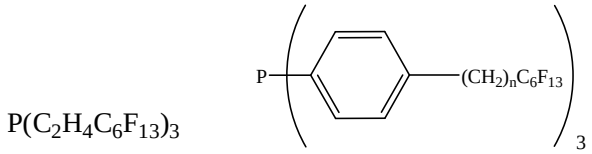
Recently, Union-Carbide has reported a separation technique that utilizes monosulfonated triphenylphosphine (TPPMS). This technique may be useful for the hydroformylation of high molecular weight and less volatile alkenes such as 1-octene, 1-dodecene and styrene. The use of solublizing agents such as N-methylpyrrolidone, polyalkylene glycols etc. makes alkali metal salts of TPPMS soluble in nonpolar organic phase. This probability is due to formation of reverse micelles, aided by solublizing agents. Rh-TPPMS catalytic system can be used to hydroformylate higher alkenes in such an organic medium. At the end of reaction, the single phase is separated into nonpolar and polar phase by addition of water or methanol or by change of temperature. The catalyst remains in polar phase, while the product goes into nonpolar phase.

In recent times, a concept of ñthermoregulated phase transfer catalysisò based on cloud point of non-ionic phosphine ligand has been effectively introduced to the biphasic hydroformylation of long chain alkenes [73]. Principally, ñthermoregulated phase transfer catalysis (TPTC)ò is insoluble in common organic solvents at room temperature. On heating the catalysts becomes soluble in organic solvents indicated by the color change of the solution. Hence, at the reaction temperature of hydroformylation reaction, which is normally more than room temperature, the reaction proceeds homogeneously. After the completion of reaction i.e. on cooling to room temperature, the catalyst precipitates from organic phase, which restrains the products and can be separated from the catalyst by decantation only. Therefore, the advantage of TPTC is the combination of homogeneous and heterogeneous catalysis. Reports suggested [74] that recycling up to 20 times, both

conversion and aldehyde selectivities are comparable with fresh catalysts hence these catalysts can recycle without loss of activity towards hydroformylation.

1.7.2.2. Fluorous biphasic system

The problem of differential solubility experienced in the aqueous biphasic systems led Horvath et. al. [75] to propose the use of fluorous-organic biphasic system. Fluorous and organic solvent mix at the typical reaction temperature, which is generally, used for hydroformylation reactions, but the phase separation occurs at room temperature [76]. Using rhodium complex of **11** in a mixture of perfluorocyclohexane and toluene, Horvath showed high rates for hydroformylation of 1-octene could be obtained and the leaching of rhodium into the organic phase was very limited (4.2% after nine cycles). The l:b ratio could be high (8:1), but ~ 10% of the starting alkene was lost through isomerization. Even higher rates can be obtained if the toluene is omitted and the ligand is replaced by **12** (n = 0). In this case, rhodium leaching is reduced to 0.05% per run [77]. The lacks of toluene removes the energetic requirement for fractional distillation to separate the catalyst from the solvent.



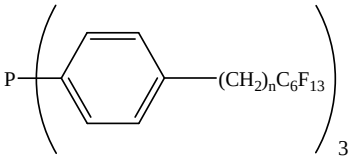
11 **12**

1.7.2.3. Supercritical carbon dioxide as a solvent

Supercritical fluids (compressed gas above their critical temperature) dissolve many low to medium polarity organic molecules and are fully miscible with permanent gas. If the catalyst can be dissolved, truly homogeneous catalysis can occur, because all participants are fully dissolved in one phase and no phase transfer problem arises. The use of supercritical carbon dioxide ($scCO_2$) as a solvent has received attention as a versatile, environmentally benign solvent for a variety of reaction. Hydroformylation of alkenes in presence of $scCO_2$ is getting a great response from engineering point of view. As a solvent in homogeneous hydroformylation catalysis, $scCO_2$ offers many advantages over conventional organic solvents as discussed below;

- Many gases exhibit higher solubilities in $scCO_2$ than in organic solvents. Hence, faster hydroformylation reactions are expected to occur within the $scCO_2$ environment.
- Conducting the reaction in single phase can eliminate the problems of slow rate of reaction of hydroformyalation since mass transfer controls the reaction rate across the gas-liquid interface.
- $scCO_2$ is non-flammable, non-toxic, environmentally friendly, cheap, readily available and has low critical temperature (T_c = 31.1^{0}C) and moderate critical pressure (P_c = 78.9 atm) and of density 0.47g ml^{-1}.
- The unusual solvent properties of $scCO_2$ may lead to increased reaction rates of selectivities due to solvent effects in homogeneous catalysis.
- The strong dependency of solubility of solutes in $scCO_2$ to temperature and pressure near critical point may be exploited in the development of efficient hydroformylation catalysts.
- Product recovery may accomplish through a small pressure change that decreases the solubility of the product so that it will separate from the solution.
- The design, scale-up and operation of reactors operating in single phase are much simpler than multiphase reactors.

However, one of the main problems in using $scCO_2$ as a solvent for homogeneously catalyzed reactions is that conventional organometallic catalysts, particularly those with aryl-containing ligands, have low solubility, which is a major obstacle for the development of this area. However, several approaches [78] have been adopted whereas the hydroformylation catalysts can be, solublize into $scCO_2$ via addition of perfuorinated chains (**13**, n = 1) to organic portion of the catalysts.



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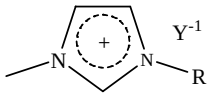
Although the supercritical solvent can very easily be removed by decompression of the gas, this does not overcome the main separation problem: that of the catalyst from the product. In an alternative process, the temperature and pressure swings takes part for

removal of catalysts and the product is then removed by decompression. This process has been successfully demonstrated for hydroformylation of with ligand such as **13** (n = 1) [78].

1.7.2.4. Ionic liquids as a solvent

Ionic liquids [79] are the salts consisting of ions, which exist in the liquid state at ambient temperature i.e. they are salt that do not normally require to be melted by means of an external heat sources. They have extremely low vapor pressure and depending on the design of the ionic liquid, it can dissolve or reject organic compounds. They are typically consisting of organic nitrogen-containing heterocyclic cations and inorganic anions such as **14**.



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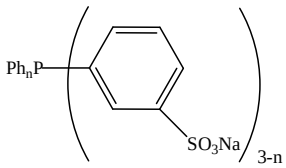
The first hydroformylation reaction has been carried out in ionic liquids using rhodium complexes of **15** (n = 2). However, conversions were low, probably because of the high lattice energies of the sodium salts make them rather insoluble in the ionic liquid [80].



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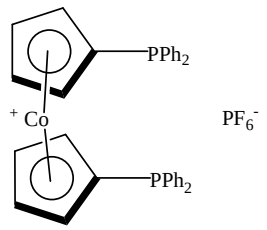
More recent work has shown excellent activity and selectivity with the ligands such as **16** [81] or **17** [82]. The product can be decanted from **14** (R = C_4H_9, Y = PF_6) or extracted with nonpolar organic solvents. For ligand **17**, high rates and selectivities with minimal leaching (<5 ppb) are obtained in the ionic liquid **14** (R = C_4H_9, Y = PF_6) and it is possible to envisage processes involving decanting or extraction of the products into and organic solvent in a batch continuous mode.



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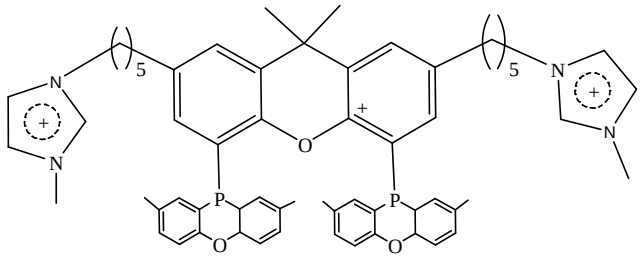

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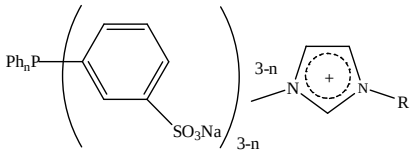
Hydroformylation of 1-hexene [83], 1-octene [84] and methyl-3-pentanoate [85] have also been successfully carried out by using ionic liquids as a solvent system. In all these cases, the conversions and selectivities are comparable with the established processes. Chauvin et al [80] have reported, the rhodium complex catalyzed 1-pentene hydroformylation in presence of various 1, 3-dialkylimidazolium salts as an ionic solvent. The results showed highest TOF for 1-pentene using ionic liquid $(BMI)^+(PF_6)^-$ (BMI = 1-n-butyl-3-methylimidazolium salt) as a solvent with Rh/PPh_3 system. Under the similar conditions, the TOF for 1-pentene got an unpredictably decrease for the Rh/TPPMS, TPPTS systems. The only thing is to take under consideration while using ionic liquids as a solvent for hydroformylation reactions is to choose appropriate inorganic anions with organic cations of the molten salts.

Another way of using ionic liquids that has potential for continuous-flow liquid operation is to support the ionic liquid as a film on a solid (such as silica, sometimes derivatized with molecules similar to the ionic liquid) and the process is known as ñsupported-ionic-liquidsò (SIL). The catalyst is dissolved in the ionic liquid film, with the advantage that the surface area of the ionic liquid is greatly enhanced relative to its volume and the substrate can readily diffuse to the catalyst. These systems have recently been used for rhodium-catalyzed hydroformylation with ligand such as **9** (n = 0) or **18** (n = 0, R = C_4H_9) in the ionic liquids **14** (where, R = C_4H_9, Y = PF_6 or BF_4). Leaching was

reduced by working at low conversions so that the polarity of the substrate/product phase was kept low to minimize catalyst extraction from the ionic liquid film [86]. One potential disadvantage of using ionic liquids containing PF_6 or BF_4 is that they react with traces of water to give species such as O_2PF_2 and HF and they very reactive and corrosive that can poison the catalyst [87].



18

1.7.2.5. Supercritical fluids-ionic liquids as solvents

An alternative to extracting products from ionic liquids with organic solvents is to combine the favorable properties of ionic liquids with those of supercritical fluids. $scCO_2$ has been shown to be miscible with certain ionic liquids [88] and will extract many organic compounds from ionic liquids [89], allowing a genuinely continuous process to be developed. An ionic catalyst is dissolved in the ionic liquid in a stirred tank reactor. The substrate (alkene for hydroformylation), syn-gas (CO and H_2) and $scCO_2$ are then passed into the reactor either, separately or mixed. The reaction takes place and the product flow out of the reactor dissolved in $scCO_2$, which is decompressed to release the products. The CO_2 containing any excess CO and H_2 can be recompressed for an emissionless and continuous process requires no separation of the products from the solvent. The first demonstration of such a system was in hydroformylation reactions [87] and showed rather low rates, but these have much improved by using ligand **13** (n = 2, R = C_3H_7) and alternative ionic liquid, **14** {R = C_8H_{17}, Y = $(CF_3SO_2)_2N$} [90].

A number of innovative solutions to the problem of separation of catalysts from products in homogeneous hydroformylation catalytic reactions have been proposed and demonstrated (Table 1.9.). Some are genuinely continuous with built-in product separation; others can be carried out in batch continuous mode, with the separation being carried out in an external chamber by a non-distillation process. All of the processes have some disadvantages, and most of them do not yet show the activity required for commercial application. The catalyst, solvent, or process may be very expensive, catalyst leaching may be too high, the solvent or ligand may be too expensive, or the pressure

may be too high. Many approaches show considerable promise, but few detailed cost analyses have been carried out. They will be essential before any commercialization can be contemplated. An important property of some of the processes may be reduced environmental impact, as a result of recycling most of the components and getting away from volatile organic solvents with their polluting properties. The environmental impact of some solvents (fluorous, ionic liquid) is, however, still unknown. However, Table 1.9. attempts to compare the variety of the separation methods including existing commercial processes for the rhodium-catalyzed hydroformylation of 1-octene.

Table 1.9. Rhodium catalyzed hydroformylation of 1-octene using variety of separation methods and catalyst systems, compared with the results from homogeneous commercial systems (first four rows) [91].

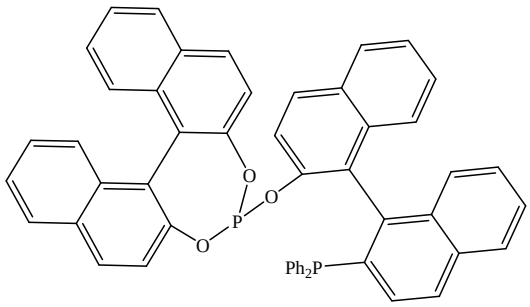
System	Ligand	Press. (bar)	Temp. (^{0}C)	TOF (h^{-1})	Rate[§]	l:b	Rh loss[!]	P loss[!]	Trouble
Homo/Co	No	300	150	38	3.2	2.3	-	-	-
Homo/Co	**14**	80	200	20	1.6	9	-	-	-
Homo*	PPh_3	15	95	770	2.0	8.8			
Homo*	PPh_3	16	110	444	0.8	5.3			
Supported	**1**	50	80	287	0.19	40	<0.1	nr	
Supported/ $scCO_2$	**1**	170	90	160	n/a	33	<1.2	nr	R, P
Soluble polymer	**3**	30	80	160	0.03	nr	0.3	nr	R, S? L
Dendrimer	**4**	10	120	1792	7.1	13.9	nr	nr	U
Supported dendrimer	**5**	67	45	25	0.03	0.05	20	nr	R, L
TRAB	**6**	50	100	182	0.3	nr	nr	nr	R, S?
Fluorous biphasic	**7**	10	100	837	0.1	4.5	0.12	nr	S, L, E
Fluorous biphasic	**8**	20	70	4400	8.8	6.3	0.08	16	E
$ScCO_2$	**8**	200	65	430	14.2	5.5	<0.1	nr	P
Ionic liquid	**12**	46	100	318	1.2	49	<0.1	nr	E
Supported ionic liquid	**13**	100	100	3600	n/a	2.4	0.01	nr	S, E?
$ScCO_2$/Ionic liquid	**13**	200	1000	8	0.12	3.1	<0.1	nr	P, S, E

Abbreviations: nr = not recorded, n/a = not applicable, [§](mol $dm^{-3}h^{-1}$), [!][mg(mol product)$^{-1}$], R = low rate, P = high pressures, S = low selectivity to linear aldehyde, L = high catalyst leaching, U = ultrafiltration not attempted, E = expensive ligand and/or solvent, *Propene, which can not isomerize, [À]1-Hexene, [#]Vinyl acetate, [Ƨ]Leaching measured for styrene, TRAB = Thermo Regulated Aqueous Biphasic.

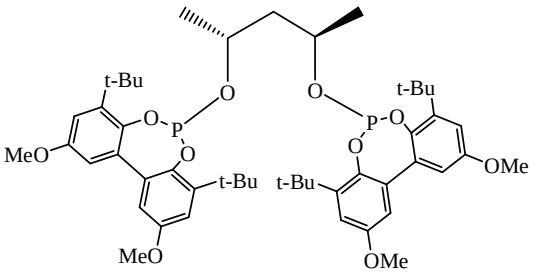
1.7.3. Asymmetric hydroformylation

Hydroformylation is a reaction that has been run for many years at large scale yet, despite its great potential in chiral synthesis; a production scale enantioselective version has so far been elusive. Achiral hydroformylation has been in industrial use since the 1940s, with a great deal of success. However, the reaction has yet to be used industrially in its asymmetric form. The first attempt to extend hydroformylation to chiral products was made in the early 1990s, with styrene as a substrate. The hydroformylation of vinyl arenes would give the nucleus of the profen class of drugs, but these are largely sold in racemic form, and those that have been switched to their single enantiomer form have low annual sales.

Limited success with asymmetric hydroformylation has been achieved on a narrow substrate range with the use of rhodium catalysts based on Takasagoôs BINAPHOS ligand. However, it is not ideal as a catalyst, as its functional group tolerance is limited, making it difficult to apply in the real world to pharmaceutical intermediates, which often have complex substitution patterns. Several other catalyst ligand systems have been explored, particularly for the hydroformylation of vinyl arenes. BINAPHOS gives an ee of 97%, but a branched:linear ratio of only 7:1 for the asymmetric hydroformylation of styrene. While CHIRAPHITE from Union Carbide, gives a lower ee of 88%, the branched: linear ratio is much better at 50:1.



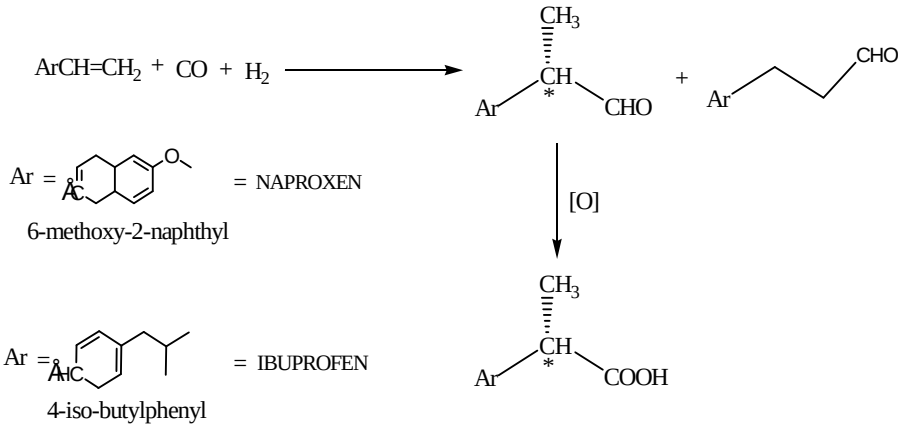
(*R, S*)-BINAPHOS



(*R, R*)-CHIRAPHITE

Significant innovations [92] in asymmetric hydroformylation provide potential routes to enantiomerically pure biologically active compounds have occurred. Particularly for the preparations of non-steroidal anti-inflammatory (NSAI) pharmaceuticals such as Naproxen and Ibuprofen.

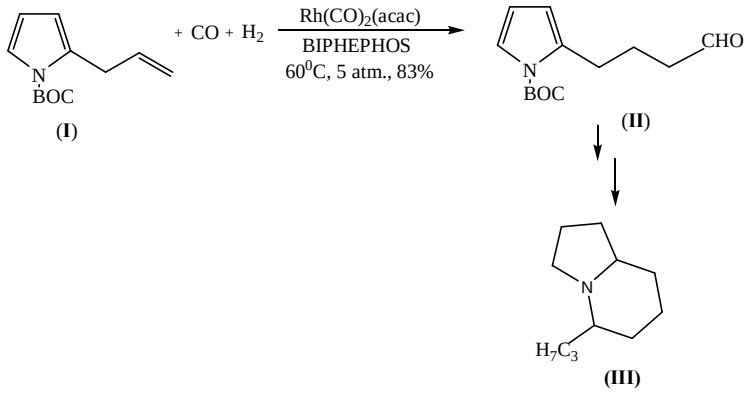
These compounds can be obtained via initial enantioselctive hydroformylation of the appropriate vinyl aromatic to branched chiral aldehyde and subsequent oxidation (Scheme 1.5.). High optical yield (up to 82% ee) of enantiomeric *α*-methylarylacetaldehydes have been obtained from styrene, *p*-isobutylstyrene, 2-vinylnaphthalene and 2-mthyl-6-methoxynaphthalene [93] by using a $PtCl(SnCl_3)L^*$ catalyst (where L* is chiral ligand). However, the regioselectivity of these catalysts and the rate of reaction were low. Certain chiral biphosphite modified rhodium catalysts [94] have been reported to give the desired NSAI pharmaceutical precursors at high regioselectivity, rate and enantioselectivity. High enantioselectivities and regioselectivities have been obtained using both mono- and 1,2 disubstituted prochiral alkenes employing chiral phosphine phophites modified rhodium catalysts.



Scheme 1.5. Hydroformylation steps involved in the production of NAPROXEN and IBUPROFEN

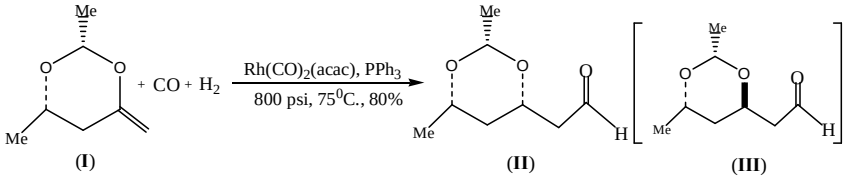
Moreover, hydroformylation is being used for the synthesis of Vitamin A, developed by the BASF AG. Although it is a Witting-type coupling reaction between vinyl-*β*-ionone (C_{15}) and *γ*-formylcrtyl acetate (C_5), there is an early hydroformylation step: 1-vinylethylenediacetate is hydroformylated under high-pressure conditions to yield the branched aldehyde with regioselectivities of up to 75%. This intermediate is then transferred into *α*, *β*- unsaturated derivative that couples with the C_{15}-ylide building block to form the C_{20} vitamin-A [95]. An alternative Hoffmann-La Roche procedure also includes a hydroformylation step [96]. These two processes share most of the Vitamin A world capacity of approximately more than 2500 tons per year.

The regioselective formation of linear aldehydes is important in industrial process. The ligand BIPHEPHOS developed by Union Carbide, gives the highest ratio of *n*-butanal from propylene. This ligand is useful for regioselective formation of linear aldehydes from various functionalized 1-alkenes under mild conditions. The linear aldehyde (II) was obtained from (I) and converted into indolizdine alkaloid (III) [97] (Scheme 1.6.).



Scheme 1.6.

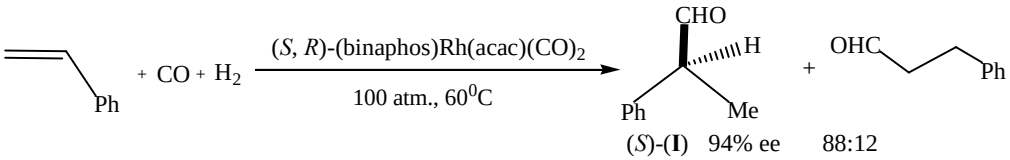
The hydroformylation of enol ethers affords *β*-hydroxy aldehydes, which can be further extended to catalytic aldol synthesis. The Rh-catalyzed hydroformylation of the cyclic enol ether (I) affords [98] the protected *syn*-3, 5-dihydroxyaldehyde (II) without forming the *anti*-product (III) (Scheme 1.7.).



Scheme 1.7.

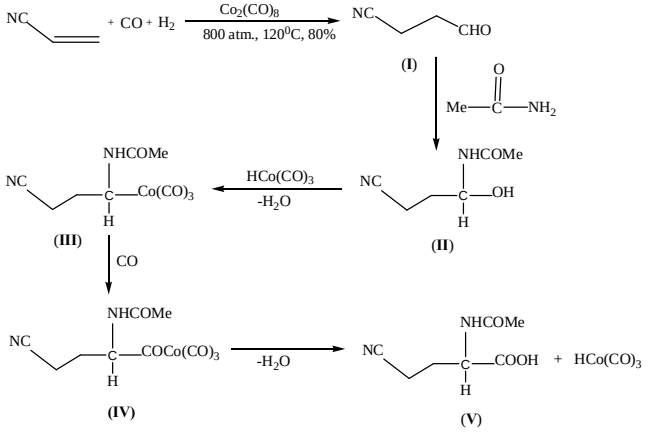
Enantioslective hydroformylation has also been attempted using various chiral ligands [99]. Highly enantioslective Rh-catalyzed hydroformylation of some terminal alkenes has been achieved using the chiral phophine-phosphite ligand (*R*)-[2-(diphenylphosphino-1,1ô-binaphthal-en-2ôyl)-(*S*)-1, 1ô-binaphthalen-2,2ô-yl] and its enantiomer (*S, R*)-BINAPHOS. Hydroformylation of styrene with chiral catalyst afforded the branch aldehyde (I) (Scheme 1.8.) as the main product with 94% ee. However, the linear

aldehyde is obtained as the main product from 1-hexene with this ligand, and there is no possibility of asymmetric hydroformylation [100].



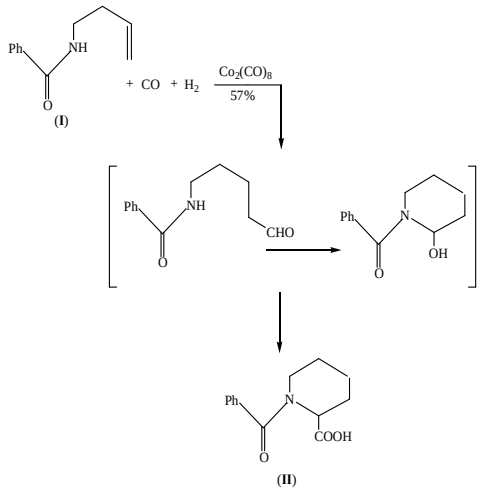
Scheme 1.8.

Cobalt-catalyzed carbonylation of aldehydes in the presence of amides gives rise to acylamino acid. The reaction is called Wakamatsu reaction [101]. Hydroformylation of acrylonitrile in presence of acetamide affords the linear aldehyde (I) (Scheme 1.9.**)**. The hydroxyl amide (II) formed from the aldehyde (I) and the amides are converted to acylcobalt complex (III) by dehydration. Insertion of CO generates the acylcobalt complex (IV) from (III), which reacts with water to give the acylamino acid **50** and regenerates hydrocoblatcarbonyl species. Acylamine acid **50** are prepared in one pot from alkene by hydroformylation, followed by Wakamatsu reaction. It should be noticed that amino acid (V) (Scheme 1.9.**)** are formed by the reaction of water generated during the reaction with acylcobalt complex (IV), rather than aldehyde, even though the reaction is carried out under hydrogen pressure.



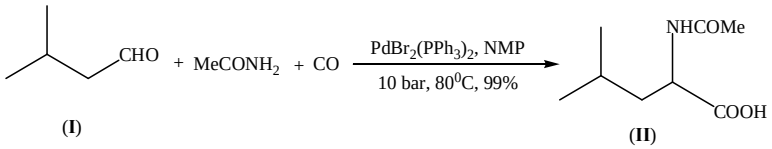
Scheme 1.9.

As an intramolecular version, N-benzoylpipecorinic acid (II) was prepared by the reaction of N-benzoyl-3-butnylamine (I) (Scheme 1.10.) [102].



Scheme 1.10.

The Wakamatsu reaction is also catalyzed by Pd catalysts such as $PdCl_2(PPh_3)_2$ and Pd/C. Formation of amino acid (II) from 3-methylbutanal (I) is an example (Scheme 1.11.) [103].



Scheme 1.11.

Recently, Dowpharma (a unit of Dow Chemical Company) has announced new capabilities in catalytic asymmetric hydroformylation (AHF) of olefins that have significant applications in the development and manufacture of pharmaceutical intermediates. They reported that AHF is a powerful technology that combines the creation of a chiral center with the introduction of versatile aldehyde functionality. Among its many benefits, AHF:

- Enables a more efficient and cost-effective manufacturing system that produces far less waste.
- Shortens the route to drug development by capitalizing on AHFôs versatile aldehyde functionality.
- Avoids inefficient drug separation technology.

1.7.4. Molecular modeling in hydroformylation reactions

Koga et al. [104] studied the hydroformylation of ethylene via HRh(CO) (PH3) catalyst (less selective towards aldehydes). The PE (Potential Energy) surface area was evaluated by the HF (Hartree-Fock) level using effecting core potential of rhodium. Additionally, intermediate and transition-state geometries were calculated at the MP2 (second order Moller-Plesset perturbation) level with an extended basis set. The MP2 results clearly show that considering electron correlation is major importance when treating catalytic reactions involving transition metals, even qualitatively: for example, the ethylene binding energy from the HF calculation is only 2.9 kJ/mol whereas MP2 yields energy of as much as 114.9 kJ/mol. At the same level of theory, Koga et al. also studied the insertion of ethylene into metal-hydride bond and the Berry pseudorotation pathways of pentacoordinated complex. The lowest transition state was found on the path describing a Berry pseudorotation of a virtual square-pyramidal complex with both hydride and olefin in basal positions. Considerations of orbital interactions suggest that insertion into the equatorial position is unfavorable This had also been found by Hoffmann et al. [105] for analogues platinum species from extended Huckel (EHMO) calculations.

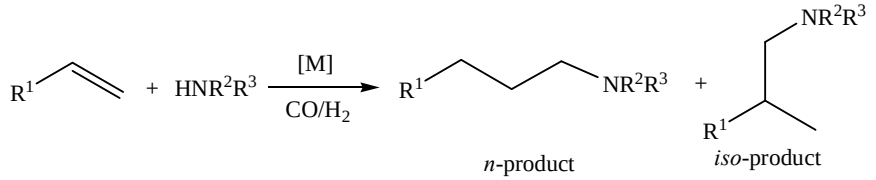
Hermann and co-workers [106] demonstrated that a number of individual conformations could be found for large and flexible chelating ligands. Using a more elaborate force field, they performed molecular dynamics simulations to sample conformational space. Each conformation corresponds to an individual minimum of steric strain energy and thus care has to be taken that the global energy minimum is located for the determination of natural bite angle.

1.7.5. Hydroformylation related reactions of carbon monoxide

Aldehydes produced via hydroformylation usually are not the final products. Due to versatile chemistry of aldehyde groups, they are further converted via reduction, oxidation or other reactions to give many useful products. Therefore, following trend in organic chemistry, hydroformylation can also be integrated in tandem or domino reaction sequences. In the present section, examples of the reactions involving initial hydroformylation and additional conversions of the intermediates or the aldehyde product (not in great detail) are compiled.

1.7.5.1. Hydroaminomethylation and aminocarbonylation reactions

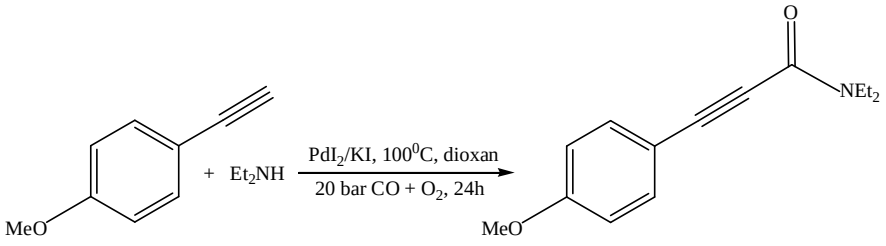
Hydroformylation of alkenes in the presence of amines can lead to an overall ñhydroaminomethylationò if the initial hydroformylation of alkene is followed by condensation of the intermediate aldehyde with primary or secondary amine to form an enamine or imine, respectively, and a final hydrogenation give a saturated secondary and tertiary amine.



Scheme 1.12.

The selective synthesis of linear amines from internal olefins or the mixtures was achieved though a rhodium/phosphine catalyzed by one-pot reaction, consisting of an initial olefin isomerization followed by hydroformylation and reductive amination [107]. The significance of atom efficient one-pot synthesis of linear amines from internal olefins has been put in perspective [108]. Hydroaminomethylation of terminal as well as internal aliphatic olefins with various amine yields in the presence of [Rh(COD)(Imes)Cl] as a catalyst. Excellent yields and high chemoselectivities were obtained in THF at 85-105^{0}C using 0.1 mol % of catalyst [109]. Highly selective phosphine modified rhodium catalyzed enamine synthesis from olefins is reported [110]. In the presence of various phosphine ligands, especially those of XANTPHOS, cationic rhodium catalysts were found to be useful for highly selective hydroaminomethylation of olefins [111].

Palladium iodide/KI-catalyzed oxidative aminocarbonylation of 1-alkynes was found to occur at 100^{0}C and under 20 bar of 4:1 mixture of CO and air [112].

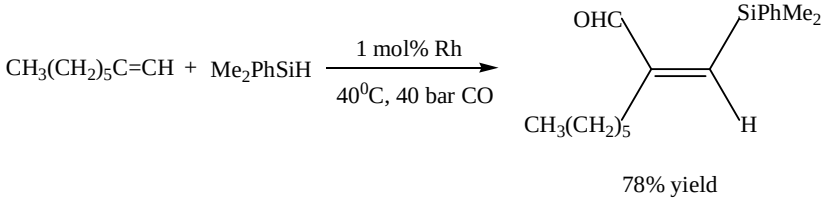


Scheme 1.13.

The use of $[BMIM]^+[BF_4]^-$, $[BMIM]^+[BF_6]^-$ and $[EMIM]^+[BF_4]^-$ ionic liquids as solvent in homogeneous palladium catalyzed aminocarbonylation of 17-iodo-5-Ŭ-androst-16-ene at 100^0C and atmospheric carbon monoxide pressure was also investigate. It was found that after the extraction of the product from toluene, the ionic liquid-catalyst mixture can be recycled several times [113]. Carbonylation reactions of allene in alcohols and amines in the presence of $Ru_3(CO)_{12}$ precatalyst gave methacrylates and methacrylamides, respectively up to 89% yield with an atom economy of 100% [114].

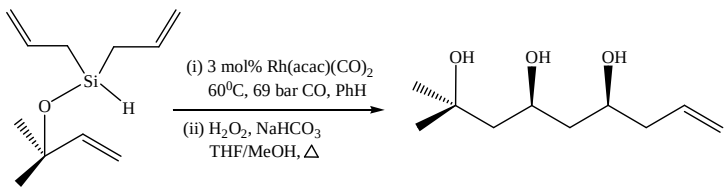
1.7.5.2. Silylformylation and silylcarbocyclyzation reactions

The zwitterionic rhodium complex $[Rh^+(CO)(\eta^6\text{-}C_6H_5BPh_3)^-]$ in $[BMIM]^+[PF_6]^-$ ionic-liquid was found to catalyze the biphasic stereoselective silylformylation of 1-alkynes with Me_2PhSiH under either a CO or synthesis gas atmosphere with excellent catalyst recycling [115] (Scheme 1.14.).

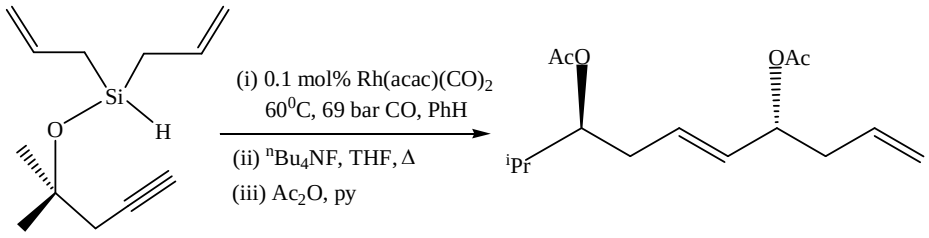


Scheme 1.14.

Tandem intramolecular silylformylation-alkyl(crotyl)silylation reactions were developed both for alkene (Scheme 1.15.) and alkyne (Scheme 1.16.) substrates having dillylsilane subsistent to obtain 1,3,5-triols or 1,5-diols respectively in a very efficient manner [116]. This tandem silylformylation-crotylsilylation reaction was used as key step to establish the C(23)-C(27) 1,5-syn-diol in this synthesis of the C(15)-C(30) fragment of dolabelides [117].

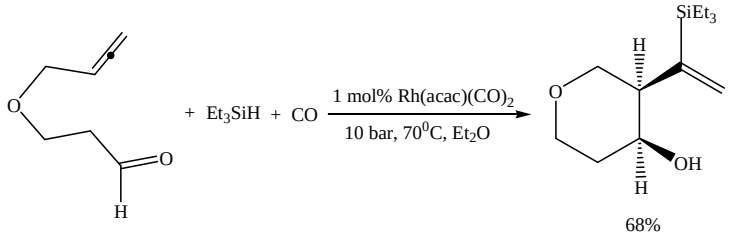


Scheme 1.15.



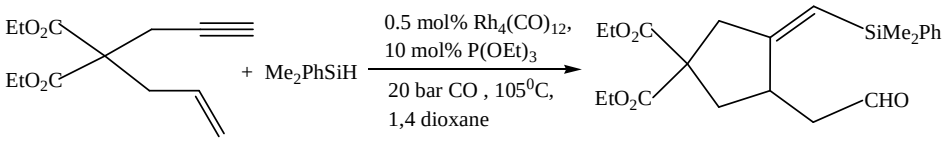
Scheme 1.16.

The synthesis of *cis*-2-triethylsilylvinylcyclopentnols and cyclohexanols from allenyl-aldehydes and ketones with Et_3SiH through rhodium-catalyzed silylcarbocyclization was also described (Scheme 1.17.) [118].



Scheme 1.17.

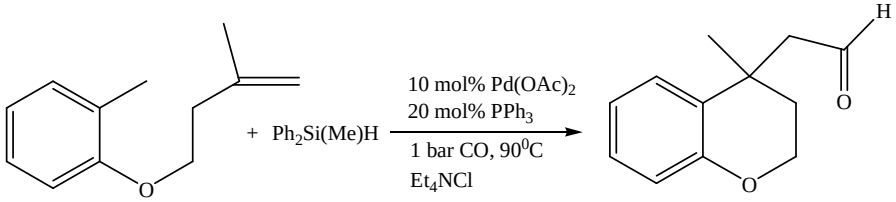
In another example, the rhodium-catalyzed silylcarbocyclization reaction of 1,6-enynes was found to afford the sole product up to 91% isolated yield (Scheme 1.18.) [119].

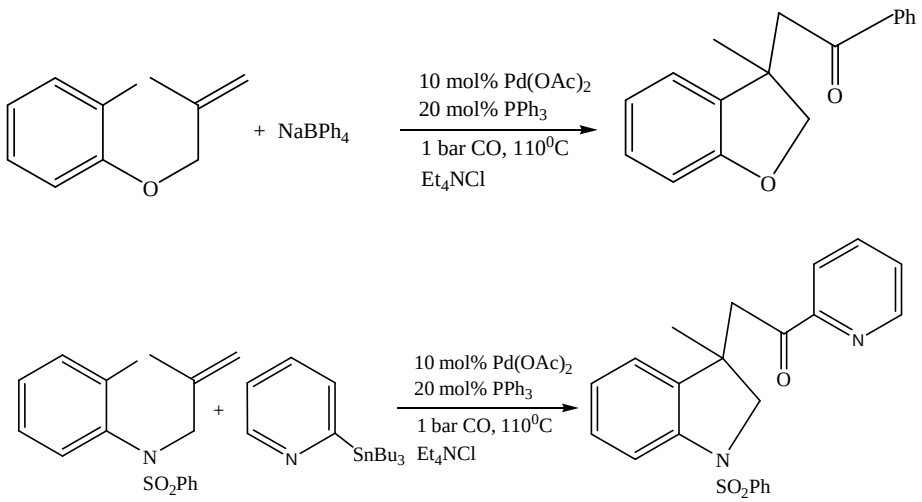


Scheme 1.18.

1.7.5.3. Cyclocarboformylation, hydroxycarbonylation and alkoxycarbonylation reactions

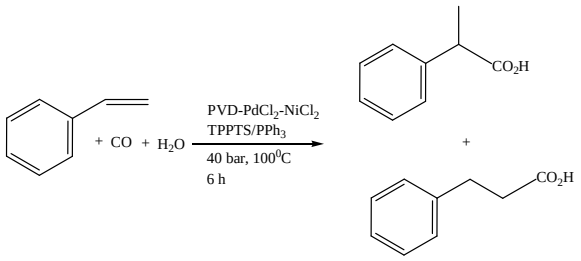
Interesting analogues of hydroformylation, namely palladium-catalyzed cyclocarbo-formylation processes were found to provide a wide variety of products depending on the substrate and reagents (Scheme 1.19.) [120].





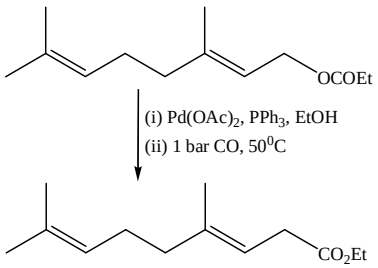
Scheme 1.19.

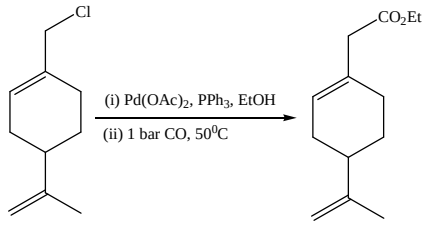
The polymer supported bimetallic catalyst system PVD-$PdCl_2$-$NiCl_2$/TPPTS/PPh_3 (PVD = polyvinylpyrrolidone) was found to have good activity in the hydroxycarbonylation of styrene under aqueous-organic two-phase condition and can be reused four times with little loss of catalytic activity (Scheme 1.20.) [121].



Scheme 1.20.

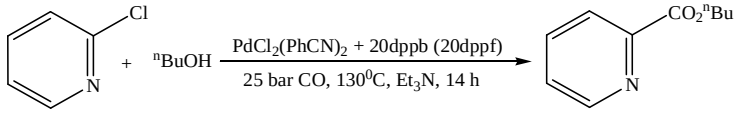
Palladium-catalyzed alkoxycarbonylations of terpenic allylic carbonates and chlorides were found to proceed with high selectivity under mild conditions to afford β, γ-unsaturated esters (Scheme 1.21.) [122].





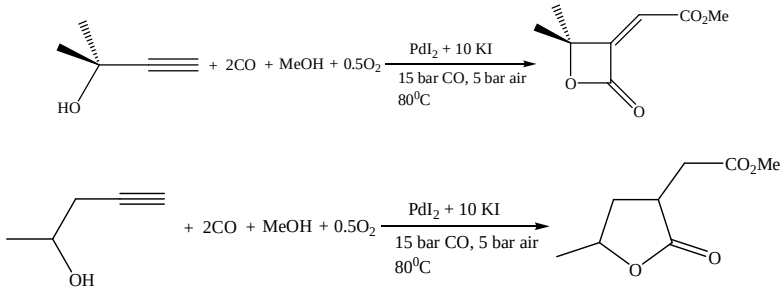
Scheme 1.21.

The palladium-diphosphine catalyzed alkoxycarbonylation of various N-heteroaryl chlorides has been examined. Among the different ligands tested, 1,4-bis(diphenylphosphino)-butane and 1,1ô-bis(diphenylphosphino)ferrocene were found to lead to the most efficient palladium catalyst systems for the conversion of 2-chloropyridines and similar heteroaryl chlorides into the corresponding butoxyesters (Scheme 1.22.) [123].



Scheme 1.22.

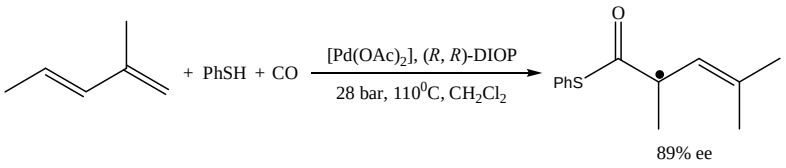
In another example, a simple catalytic system of palladium(II) was found to be a suitable for the direct one-step synthesis of a variety of heterocyclic ester-derivatives in an oxidative cyclization-alkoxycarbonylation reaction from alkynes (Scheme 1.23.) [124].



Scheme 1.23.

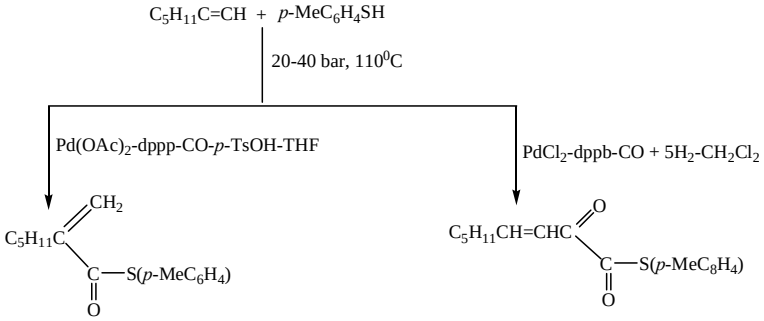
1.7.5.4. Thiocarbonylation reactions

Asymmetric thiocarbonylation of prochiral 1,3-conjugated dienes with thiophenol and CO for the synthesis of optically active ß, ɔ-unsaturated thiols esters has been developed by using a catalyst system based on [$Pd(OAc)_2$]/(R, R-DIOP) in presence of methylene chloride (Scheme 1.24.) [125].



Scheme 1.24.

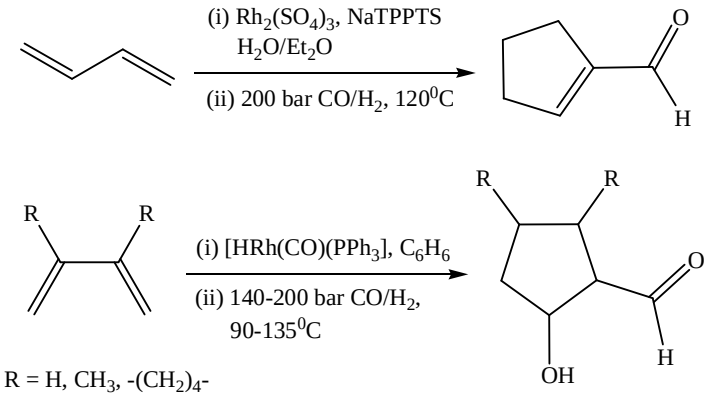
The regioselectivity of the thiocarbonylation of terminal acetylene with arylthiols catalyzed by palladium(II) and diphosphine ligands was investigated and the catalytic systems afforded excellent yields of thioesters up to more than 80% (Scheme 1.25.) [126].



Scheme 1.25.

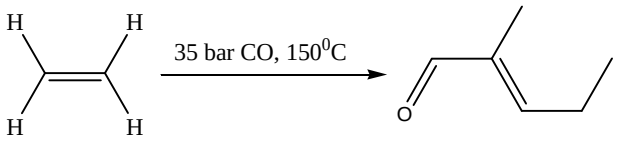
1.7.5.5. Hydroformylation-aldol reactions

The aldol reaction is reported during the hydroformylation of 1,3-butadiene forming formylcyclopentenes or 2-hydroxyformylcyclopentnones in the presence of rhodium based catalytic systems under hydroformylation reaction conditions (Scheme 1.26.) [127-128].



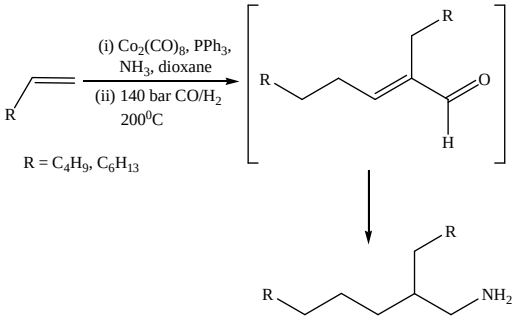
Scheme 1.26.

Reaction of ethylene and carbon monoxide in the presence of $Ru_3(CO)_{12}$, $M(CO)_6$ (M = Cr, Mo, W), KI CsOH, MeOH and water gives 2-methylpent-2-enal as the major product (Scheme 1.27.) [129].



Scheme 1.27.

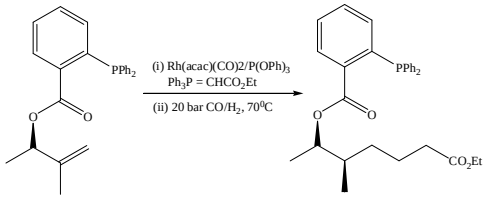
1-Hexene, and 1-octene react in the presence of $Co_2(CO)_8$ and ammonia under hydroformylation conditions to aldol condensation products that undergo consecutive reductive amination leading to saturated, primary amines (Scheme 1.28.) [130].



Scheme 1.28.

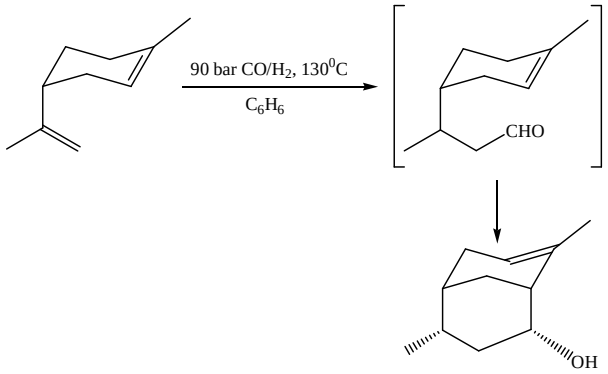
1.7.5.6. Miscellaneous other hydroformylations with additional C-C bond formation reactions

Hydroformylation in presence of stable phosphorous-ylids undergoes to a tandem Witting reaction procedure with the olefin formation from the oxo aldehyde. This procedure with a consecutive hydrogenation of the resulting olefin was used in diastereoselective hydroformylation/Witting olefination/hydrogenation sequence starting from derivative of methallylic alcohol to give the saturated products (Scheme 1.29.) [131].



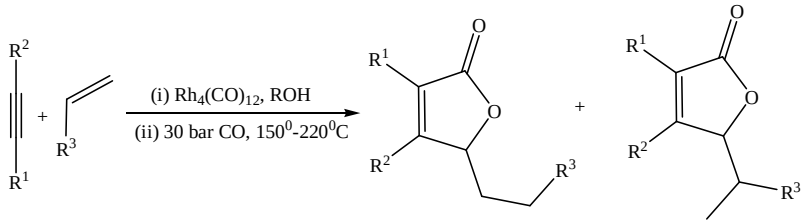
Scheme 1.29.

In an interesting example, hydroformylation can also be combined with a carbonyl ene reaction. This reaction sequence is observed in rare cases if nonconjugated olefins selectively are hydroformylated at one double bond and the resulting aldehyde can react with a remote double bond. The conversion of limonene in a one-pot reaction forms two diastereoisomers of alcohol using $PtCl_2(PPh_3)_2/SnCl_2/PPh_3$ or $PtCl_2$(diphosphine)-$/SnCl_2/PPh_3$ systems (Scheme 1.30.) [132].



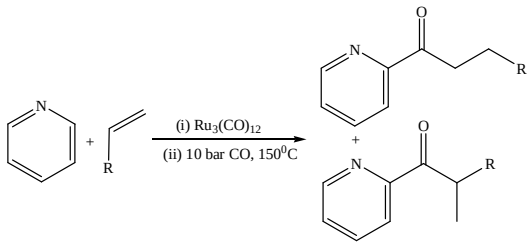
Scheme 1.30.

Rhodium carbonyl complex catalyzed reactions of internal acyetylenes with ethylene and CO in protic solvents (ethanol) as a hydrogen source, give 3,4-disubstituted 5-ethyl-2(5H)-furanones (Scheme 1.31.) [133].



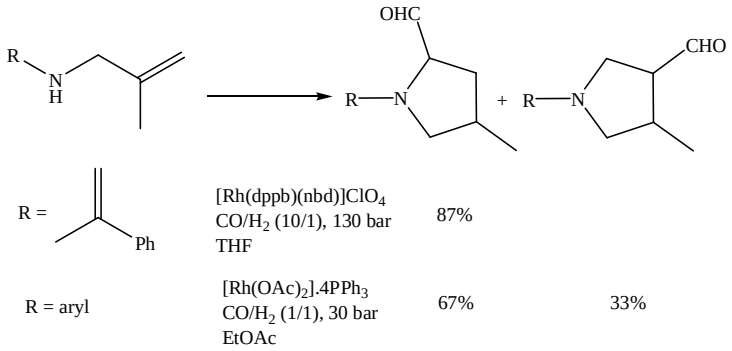
Scheme 1.31.

Hydroformylation can also be combined with CH-bond activation and ketone formation. The reaction of olefins with CO under ruthenium carbonyl catalysis in pyridine leads to a mixture of pyridyl ketones favoring linear products (Scheme 1.32.) [134].



Scheme 1.32.

A reaction sequence starting from *N*-methylallyl amides or *N*-methylanilines, respectively, is reported to proceed via hydroformylation of the olefinic double bond and consecutive intramolecular enamine condensation, followed by a further hydroformylation of an enamine double bond and resulting 2,3-formylpyrrolidines (Scheme 1.33.) [135-137].



Scheme 1.33.

1.8. Aims and scopes of present thesis

The present thesis is aimed to investigate the various aspects of the catalysts for hydroformylation reactions of propylene, ethylene and 1-hexene.

Chapter 2 is related to the activity of the central metal hydroformylation catalytic complex. The chapter 2 investigates the exact reasons for the low activity of non-rhodium complex catalysts such as dichlorotris(triphenylphosphine)ruthenium(II), $RuCl_2(PPh_3)_3$, complex for the hydroformylation of propylene under mild pressure conditions, even though, the kinetics, equilibrium and thermodynamics of interaction of carbon monoxide, CO, with $RuCl_2(PPh_3)_3$ were found to be favorable for the complexation reaction.

Chapter 3 is focusing on the ligand aspects of hydroformylation catalytic system. In the area of hydroformylation research, triphenylphosphine (PPh_3) is most cited ligand and the literature is almost silent on the effects of other Group V ligands such as

triphenylarsine ($AsPh_3$) and triphenylantimony ($SbPh_3$). Therefore, Chapter 3 includes a comparative study of transition metal catalyzed hydroformylation of 1-hexene and ethylene using rhodium, cobalt and ruthenium complexes of PPh_3, $AsPh_3$ and $SbPh_3$ as catalysts.

Chapter 4 concerns with the kinetic and mass-transfer aspects of hydroformylation reaction and extends the studies of Chapter 3. As it was observed that, the hydroformylation activity of $Rh/AsPh_3$ systems was comparable and even higher under some experimental conditions than that of Rh/PPh_3 systems. The only significant difference was the higher normal/iso (n/iso) ratio of aldehydes formed for Rh/PPh_3 systems than $Rh/AsPh_3$ system. The kinetic and mass-transfer studies have been carried for the hydroformylation of 1-hexene using $Rh/AsPh_3$ catalytic system in order to understand the reasons for the lower values of n/iso ratio of aldehydes obtained than Rh/PPh_3 system. The Chapter 4 is the first report of detailed kinetic and mass-transfer studies in the hydroformylation reaction for non-phosphine ligand such as $AsPh_3$.

Chapter 5 is deals with the development for the eco-friendly multi-functional catalyst system for hydroformylation reactions wherein heterogeneous catalyst with an ability to carry out hydroformylation and aldol condensation in a single step reaction. Industrial production of $C_{2(n+1)}$-aldol derivatives from C_n-alkene (where n = 2-10) is a three stage process. In the first step hydroformylation of C_n-alkene is being carried out to produce corresponding $C_{(n+1)}$-aldehydes with the use of Rh or Co based catalytic systems. The second step $C_{(n+1)}$-aldehydes thus obtained undergoes to aldol condensation in presence of liquid base like KOH or NaOH for production of $C_{2(n+1)}$-unsaturated aldol derivative. In the third and last step $C_{2(n+1)}$-unsaturated aldol derivative is hydrogenated to saturated $C_{2(n+1)}$-aldol derivative and then subsequently to $C_{2(n+1)}$-alcohols with use of appropriate catalytic system of Ni or Cu. In the Chapter 5 of present thesis, a novel eco-friendly multi-functional catalyst system has been developed for the preparation of the saturated $C_{2(n+1)}$-aldol derivatives from C_n-alkene (where n = 2-10) in a single step reaction under hydroformylation reaction conditions. The emphasis was over C_3-olefins (i.e. propylene) since as almost 86% share of total production capacity of oxo products is based on propylene hydroformylation.

Chapter 6 includes the conclusions and summary of the studies done in the present thesis.

1.9. References

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2. C.L. Aldridge, H.B. Jonassen, *J. Am. Chem. Soc.*, **85** (1963) 886.
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