Synthesis of Intermediates by Rhodium-Catalyzed Hydroformylation

By Hardo Siegel and Walter Himmele[*]

Dedicated to Professor Matthias Seefelder on the occasion of his 60th birthday

The reaction of olefins with carbon monoxide and hydrogen to give aldehydes is referred to as hydroformylation (oxo reaction). As catalyst for this reaction rhodium is about three to four orders of magnitude more active than the more commonly employed cobalt. With special rhodium compounds, *e.g.* di-μ-chlorobis(η-1,5-cyclooctadiene)dirhodium $[RhCl(C_8H_{12})]_2$, in the presence of chiral phosphanes, even asymmetric hydroformylations can be achieved; however, the enantiomeric purity of the products (20–30%) is not high enough for industrial-scale syntheses.

1. Introduction

The hydroformylation or oxo reaction first carried out by *Roelen* in 1938 has developed into an industrially important process for the production of aldehydes and alcohols from olefins, carbon monoxide and hydrogen[1]. The world production of hydroformylation- and secondary-products, the main ones being *n*-butanol and 2-ethylhexanol, is at present *ca.* 4.5 million t/a.

Advances made in the area of homogeneous catalysis in the last ten years, mainly through the introduction of tailor-made metal complexes, have opened up new possibilities for the synthesis of higher-purity intermediates by high-pressure and catalytic methods. One example, which is also of interest in the industrial sector, is rhodium-catalyzed hydroformylation. Since rhodium is 10^3 to 10^4 times more active than cobalt, the reaction parameters pressure and temperature can

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be widely varied, thus allowing better control of the selectivity. Olefins are transformed, usually in high yields, into aldehydes, which in turn can be converted by well-known industrially employed methods into alcohols, amines, or acids and find use in C—C coupling reactions such as condensations, Mannich, Wittig, and Grignard reactions, or ethynylations.

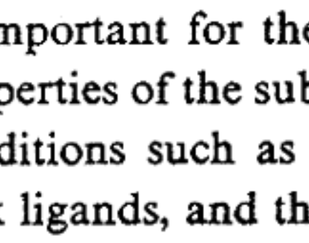
2. Selectivity of Hydroformylation with Rhodium Catalysts—Arylalkenes

In the catalytic hydroformylation of olefins with rhodium complexes the formyl group can, in principle, be inserted at each C-atom of the double bond.

$$RCH{=}CHR' \xrightarrow[\text{Rh cat.}]{CO/H_2} RCH(CHO)-CH_2R' + RCH_2-CH(CHO)R'$$

Important for the selectivity are the steric and electronic properties of the substituents R and R′, the choice of reaction conditions such as temperature and pressure, special complex ligands, and the ratio of carbon monoxide to hydrogen. In addition side reactions such as isomerization and hydrogenation, which occur in every hydroformylation, can also influence the selectivity.

On hydroformylation with rhodium catalysts (100–700 bar, 70–150 °C) with or without complex ligands on the rhodium (molar ratio <5:1), the formyl group is generally incorporated at the electron-poorest C-atom if the electronic properties of the substituents at the double bond are decisive. If, however, the steric factors dominate, then the formyl group enters at that C-atom of the double bond least shielded by substituents.

(1) 

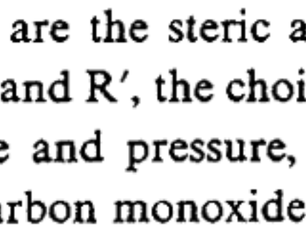
 *(2)*

Table 1. Incorporation of the formyl group in the positions a, b, c of the olefins *(1)* and *(2)* (in %).

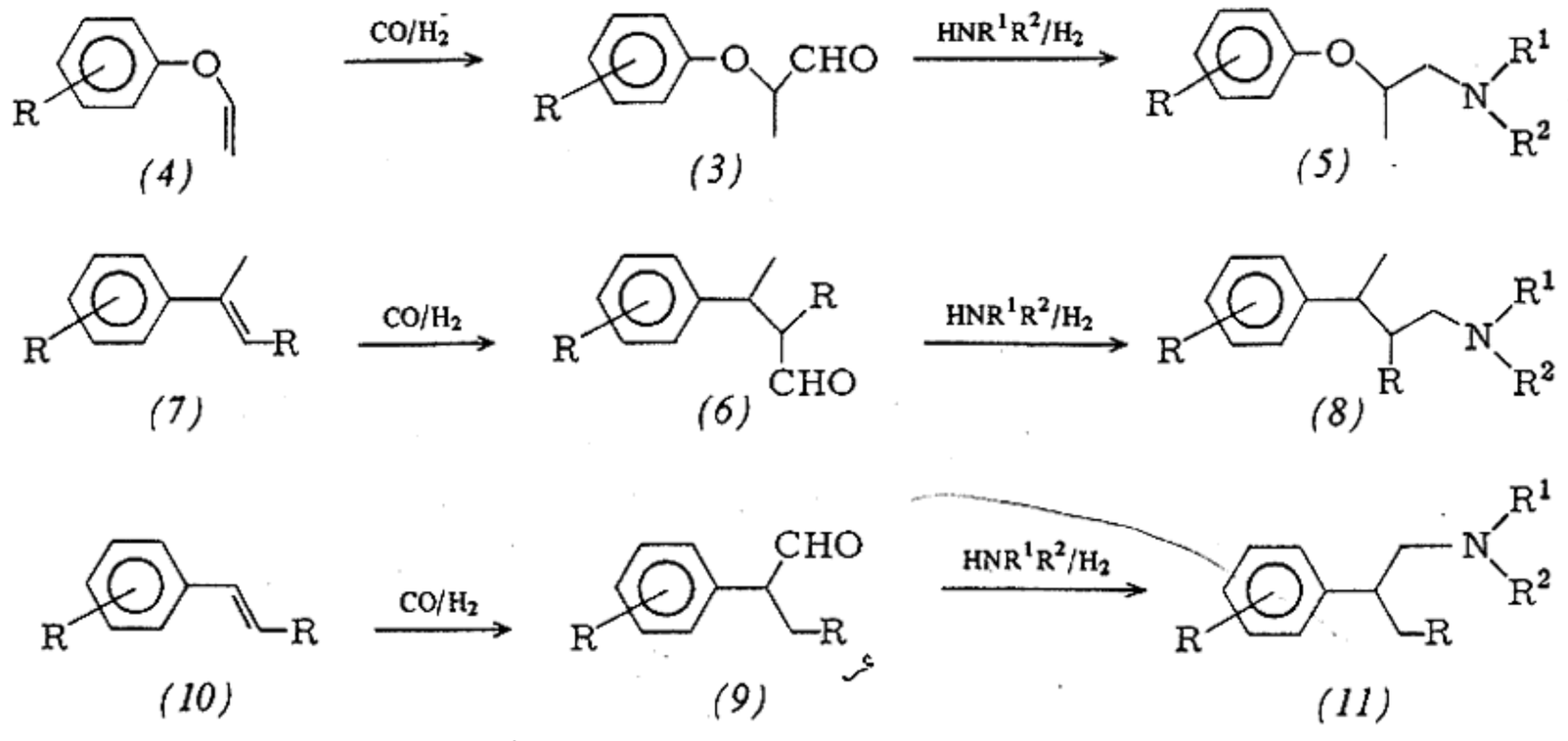
	(1)			*(2)*		
T [°C]	a	b	c	a	b	c
70	0	48	52	95	5	0
80	3	45	52	90	10	0
100	11	37	52	50	45	5
130	41	24	35	40	50	10

600 bar $CO/H_2 = 1:1$, 20 ppm Rh as $[RhCl(1,5\text{-cyclooactadiene})]_2$.

Temperature has a marked influence on the selectivity. This is immediately evident, *e.g.*, in the hydroformylation of eugenol *(1)* and isoeugenol *(2)*[2] (Table 1).

3. Intermediates for the Synthesis of Pharmacologically Active Compounds

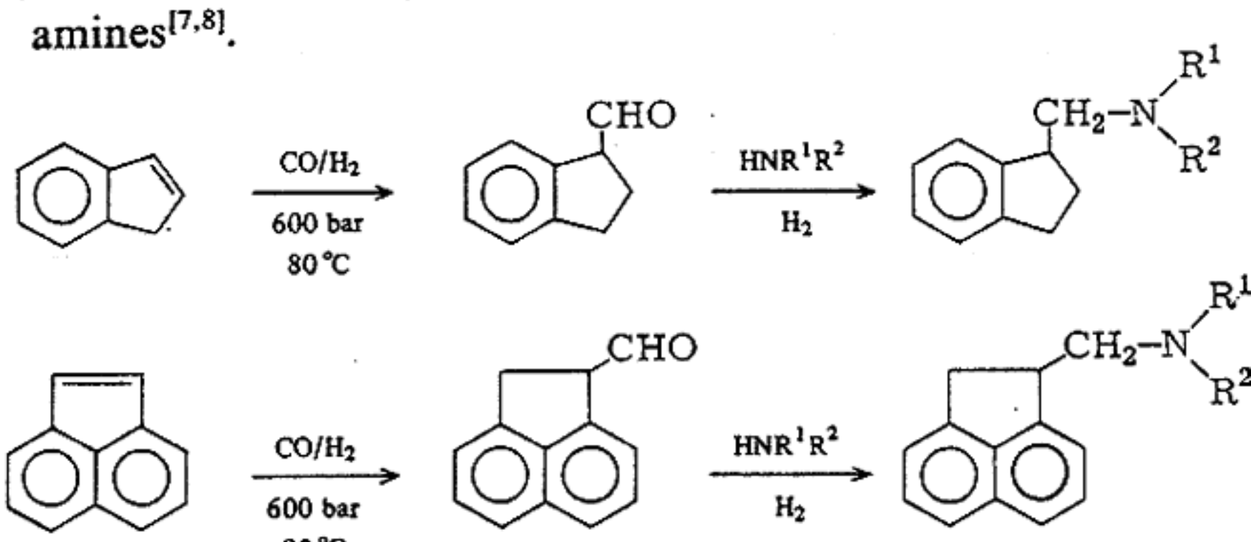
A few classes of substances which are of interest for the synthesis of pharmacologically active amines are readily accessible by hydroformylation with rhodium catalysts[3,4]. Thus, the 2-aryloxypropanals *(3)* obtained from aryl vinyl ethers *(4)* are used for the synthesis of (aryloxypropyl)amines *(5)*; 3-arylbutanals *(6)*, prepared from 2-arylalkenes *(7)*, are intermediates for the synthesis of 3-arylbutylamines *(8)*, and



2-arylpropanals *(9)*, obtained from 1-arylalkenes *(10)*, are precursors for the synthesis of β-phenylpropylamines *(11)*.

In order to achieve a high selectivity in the hydroformylation, the reaction is carried out in all cases at 600–700 bar CO/H_2 and <100 °C with rhodium concentrations in the ppm range.

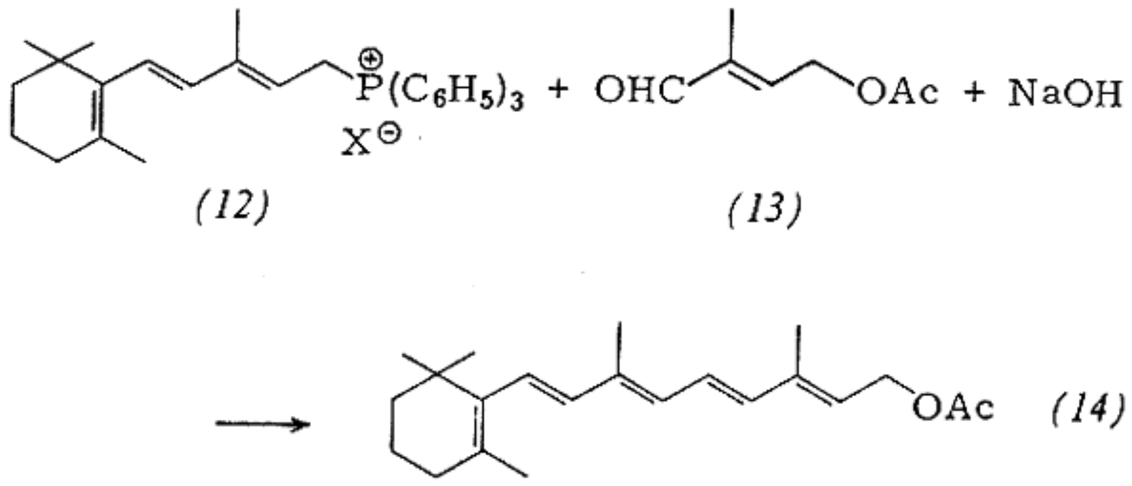
Modified β-phenylethylamines with interesting hypotensive properties are obtained by hydroformylation of indene[5] or acenaphthalene[6] in the presence of rhodium catalysts and subsequent reaction of the resulting aldehydes with amines[7,8].



4. Intermediates for Vitamin and Terpene Chemistry

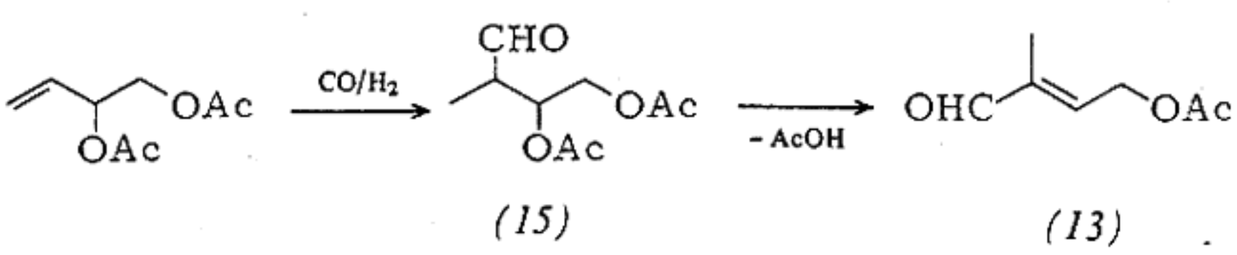
4.1. Unsaturated Aldehydes from 2-Alkenyl Acetates

In the process used at BASF for the industrial synthesis of vitamin A the ylide of a C_{15}-phosphonium salt is allowed to react with a C_5-aldehyde[9]. A phosphonium salt[11] *(12)*, prepared by reaction of vinyl β-ionol[10] and triphenylphosphane in the presence of an acid, serves as C_{15}-moiety and *trans*-3-formyl-2-butenyl acetate *(13)* as C_5-moiety. The synthesis, in presence of a base, leads directly to the vitamin A acetate *(14)*.



(12) (13) (14)

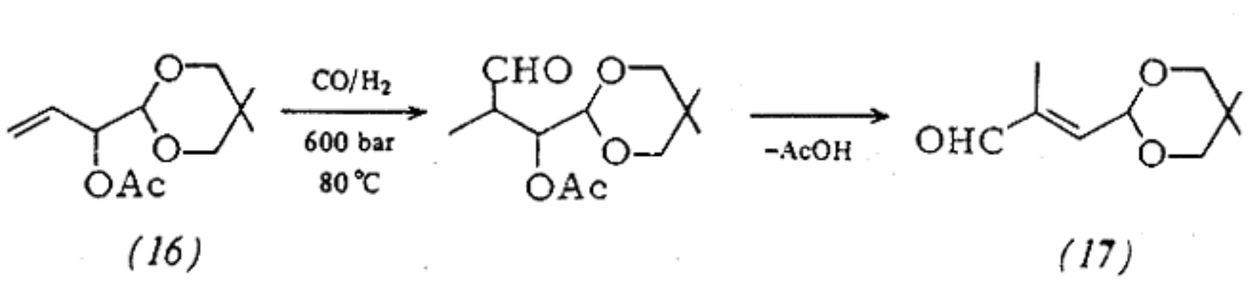
The unsaturated aldehyde *(13)* can be prepared *via* hydroformylation of 1-vinylethylene diacetate in the presence of a rhodium catalyst.



(15) (13)

High pressure and low temperature favor formation of the branched aldehyde *(15)*. At 80 °C and 600 bar CO/H_2 selectivities of up to *ca.* 80% can be achieved. The acetoxy group in the β-position to the formyl group is readily removed as acetic acid to give pure *trans-(13)*[12,13]. This synthesis of α,β-unsaturated aldehydes by hydroformylation of 2-alkenyl acetates and subsequent elimination of acetic acid can also be used for the production of further intermediates which are of interest in terpene chemistry.

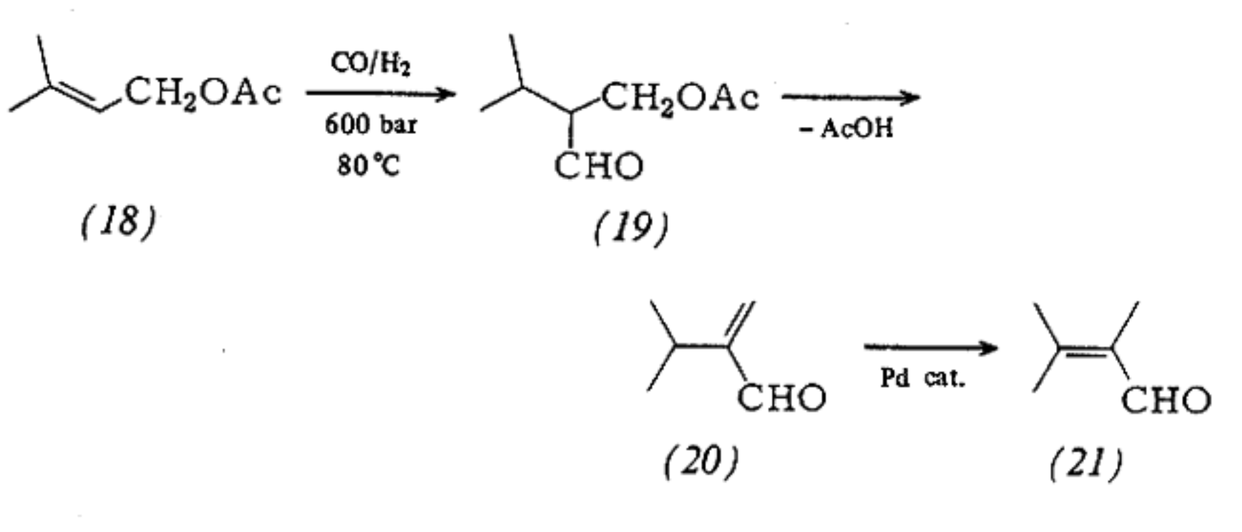
trans-2-Methyl-3-(5,5-dimethyl-1,3-dioxan-2-yl)acrylaldehyde *(17)*, an important intermediate for the synthesis of carotinoids[14], can be obtained in the same way from the acetal *(16)*.



(16) (17)

Reaction of *(17)* with the ylide of the C_{15}-phosphonium salt *(12)* and subsequent hydrolysis affords easy access to retinal (vitamin A aldehyde).

Hydroformylation of the 3-methyl-2-butenyl acetate *(18)* leads in high yields to 2-formyl-3-methylbutyl acetate *(19)*, elimination of acetic acid from *(19)* to α-isopropylacrylaldehyde *(20)*. This is isomerized in the presence of palladium catalysts to trimethylacrylaldehyde *(21)*, an important intermediate for the synthesis of irones[15].

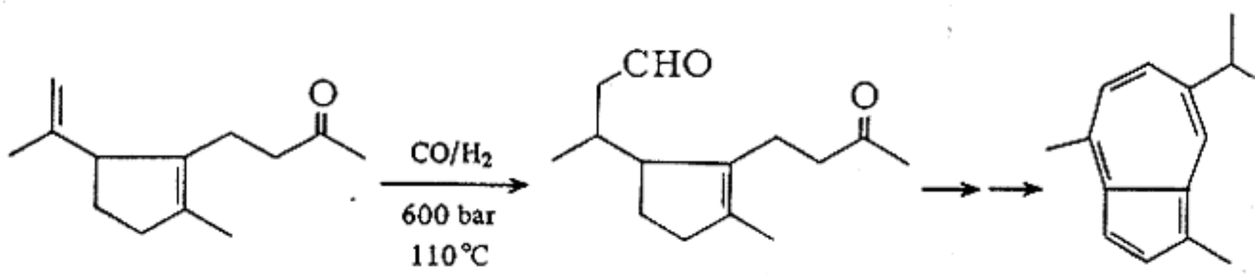


(18) (19) (20) (21)

4.2. Unsaturated Aldehydes by Hydroformylation of Non-Conjugated Diolefins

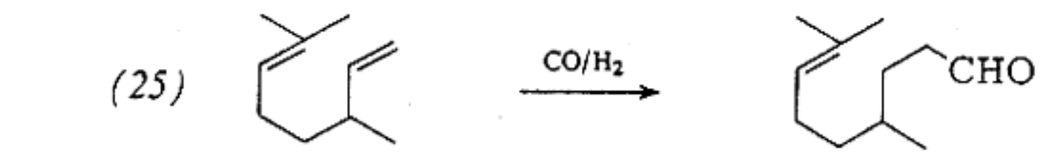
A further possibility for the synthesis of unsaturated aldehydes consists in the selective hydroformylation of non-conjugated diolefins. Here, steric factors play a decisive role regarding the degree of hydroformylation of the double bonds.

The ketone *(22)*[16] accessible from linalool is selectively hydroformylated at the isopropenyl group. An intramolecular ring closure of the resulting ketoaldehyde *(23)* followed by further reaction steps affords guaiazulene *(24)*[17].



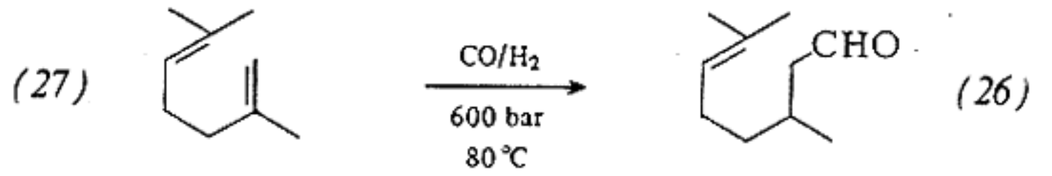
(22) (23) (24)

In citronellene *(25)* the formyl group is almost exclusively incorporated terminally (at 600 bar, 70 °C, with rhodium catalysts) owing to steric hindrance by the two methyl groups[18].



(25)

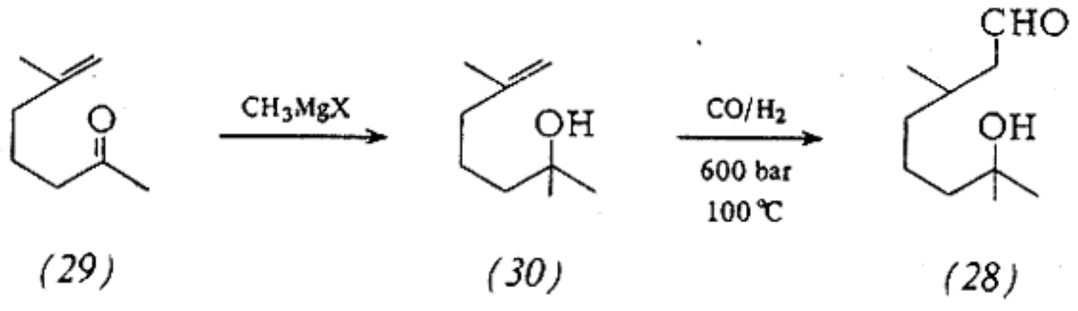
Synthesis of the industrially important citronellal *(26)* from 2,6-dimethyl-1,5-heptadiene *(27)*[19] proceeds in a similar fashion.



(27) (26)

4.3. Synthesis of Hydroxycitronellal

An industrial process for production of the important odorant hydroxycitronellal *(28)* consists in hydroformylation of the 2,6-dimethyl-6-hepten-2-ol *(30)*[20] obtainable from 6-methyl-6-hepten-2-one *(29)* *via* a Grignard reaction.



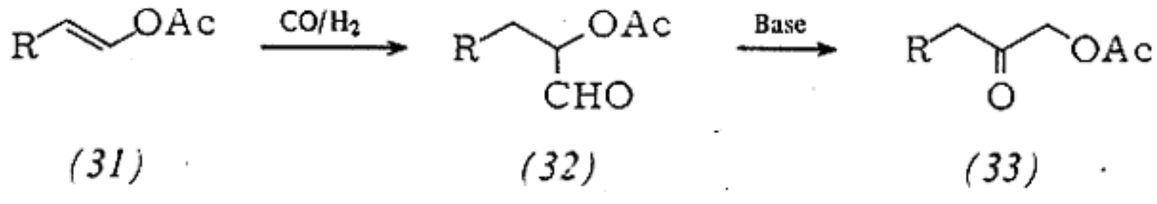
(29) (30) (28)

5. Intermediates for the Synthesis of Heterocycles

5.1. Furancarboxylic Acid Derivatives from 1-Alkenyl Acetates

In the hydroformylation of 1-alkenyl acetates *(31)*, which are readily accessible by formation of the enol acetate from the corresponding aldehydes, the formyl group is incorporated with a selectivity of >90% at the α-position to the acetoxy group [*(32)*] at 600 bar and *ca.* 110 °C.

In the presence of weak bases, *(32)* readily undergoes a type of Lobry-de-Bruyn-van-Ekenstein rearrangement to give the ketoacetate *(33)*[21].

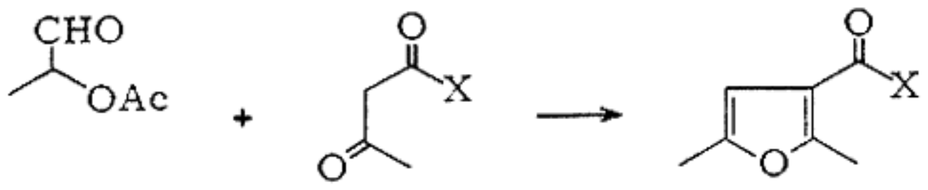


(31) (32) (33)

Hydroformylation of vinyl acetate affords 2-formylethyl acetate *(34)* in high yields. This ester, and also other 2-formylalkyl acetates, are important intermediates for a novel one-step synthesis of furancarboxylic acid derivatives.

Reaction of *(34)* with acetoacetamides *(35)* or acetoacetates *(37)* leads in high yields to the 2,5-dimethyl-3-furancarboxamides *(36)* or the corresponding esters *(38)*, respectively[22,23].

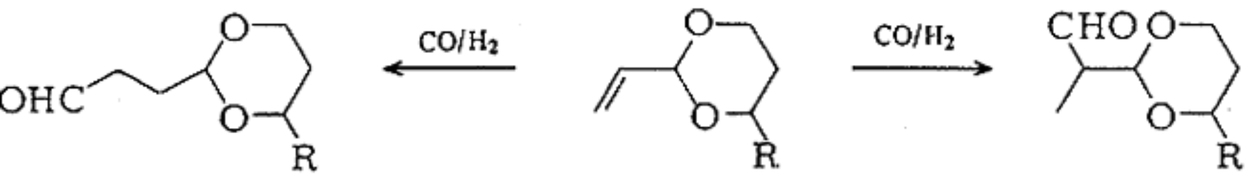
Furancarboxylic acid derivatives are of great industrial importance in seed disinfection[24] and in wood preservation[25].



(34) *(35)*, X = NR_2; *(37)*, X = OR — *(36)*, X = NR_2; *(38)*, X = OR

5.2. Pyrimidines *via* Methylmalonaldehyde Monoacetals

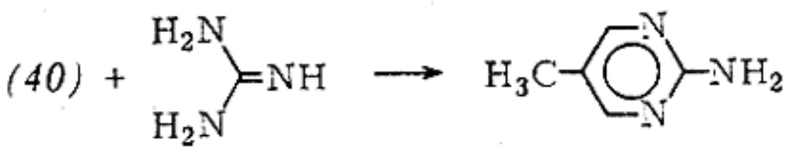
Depending on the reaction conditions hydroformylation of the cyclic acetals of acrylaldehyde *(39)* leads either to the methylmalonaldehyde monoacetals *(40)* or succinaldehyde monoacetals *(41)*.



(41) *(39)* *(40)*

When the reaction is carried out at 600 bar CO/H_2 and 80 °C in the absence of complexing agents, *(41)* and *(40)* are obtained in the ratio 25:75[26]. At 20 bar CO/H_2 and 140 °C in the presence of more than a fiftyfold excess of triphenylphosphane (referred to rhodium) the reaction product contains 70% *(41)* and 30% *(40)*. Compound *(41)* is a possible intermediate for the synthesis of 1,4-butanediol[27].

5-Methyl-2-pyrimidinylamine *(42)*, which is used as starting material for the synthesis of sulfonamides, can be readily prepared by reaction of the methylmalonaldehyde monoacetal *(40)* with guanidine.

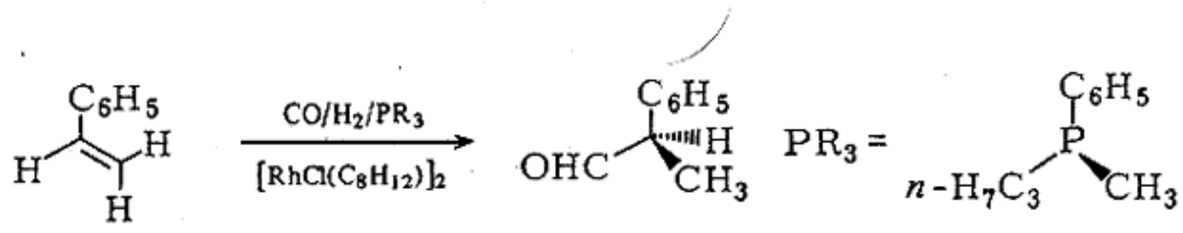


(42)

6. Asymmetric Hydroformylation with Chiral Rhodium Complexes

Horner was the first to point out that an asymmetric hydrogen transfer should be possible[29] by reaction of an optically active phosphane as ligand with one of the rhodium complexes previously found by *Wilkinson et al.*[28] to be effective catalysts in hydrogenation. Following the subsequent independent confirmation of this prediction by *Knowles* and *Sabacky*[30] and by *Horner et al.*[31], Monsanto started using this novel synthetic method on an industrial scale. *Knowles et al.* developed a method for the preparation of L-dopa by asymmetric hydrogenation of an appropriately substituted α-(*N*-acylamino)cinnamic acid[32].

Reaction of styrene *(43)* with carbon monoxide and hydrogen in the presence of *(S)*-(+)methyl(phenyl)-*n*-propylphosphane, *(S)-(44)*[33], and rhodium complex catalyst affords optically active (*R*)-(−)-phenylpropanol *(R)-(45)*[34].



(43) *(R)-(−)-(45)* *(S)-(+)-(44)*

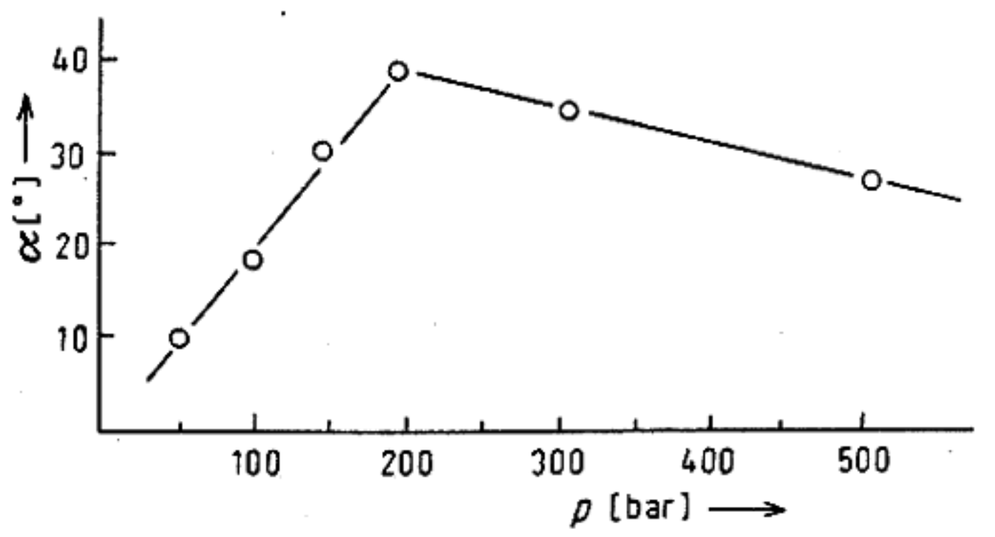
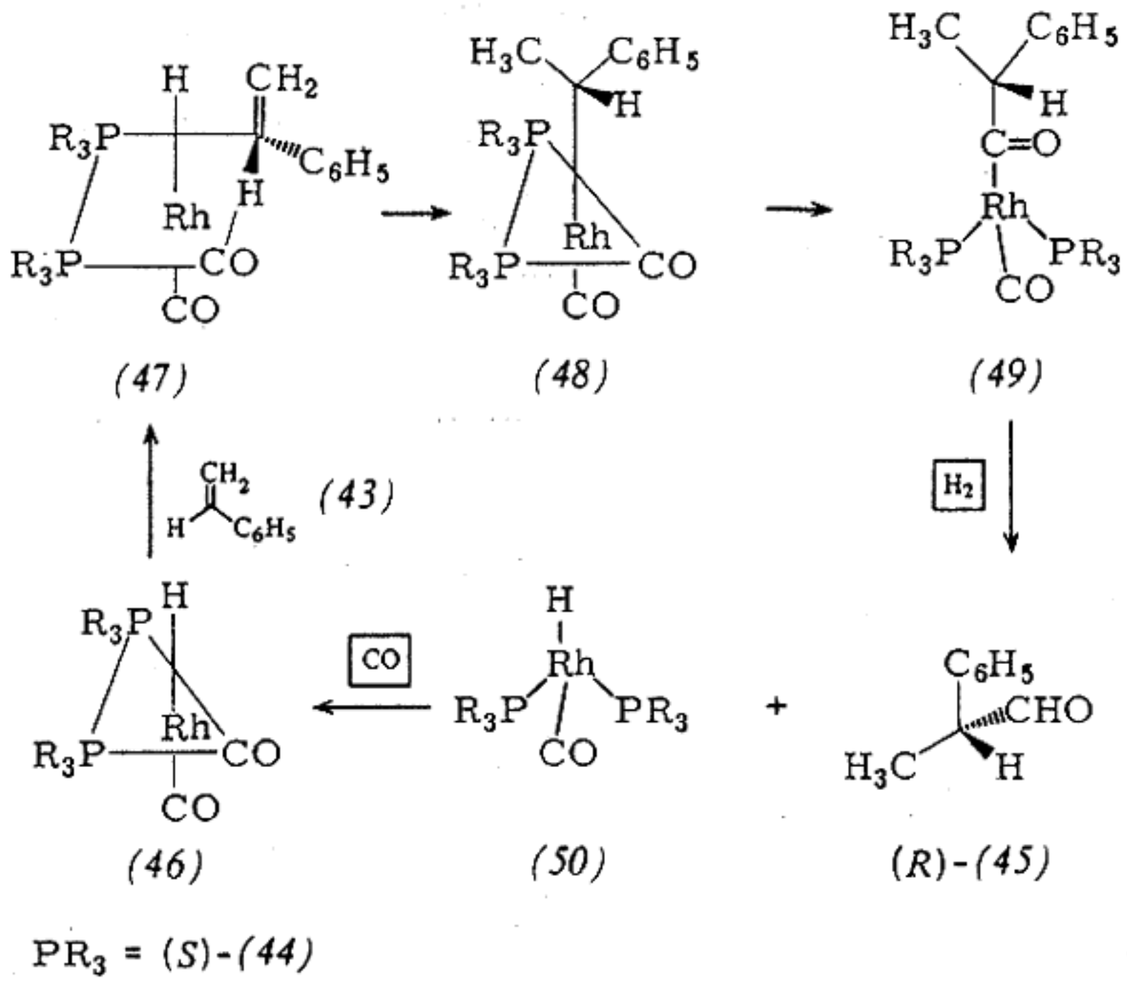


Fig. 1. Dependence of optical induction on pressure in the hydroformylation of styrene *(43)* to *(R)*-(−)-2-phenylpropanol *(R)-(45)* with di-μ-chlorobis(η-1,5-cyclooctadiene)dirhodium and *(S)*-(+)-methyl(phenyl)-*n*-propylphosphane *(S)-(44)*.

As shown in Figure 1 a noticeable enantioselective synthesis can be observed at 500 bar CO/H_2 — a proof that carbon monoxide does not completely displace the chiral phosphane from the carbonylrhodium complex, even at high pressure. In order to establish its absolute configuration, the prepared (−)-2-phenylpropanol *(45)* was oxidized by various methods to 2-phenylpropionic acid. In each case this had *R*-configuration; accordingly, *(45)* is likewise *R*-configurated. This enantionselective synthesis can best be explained in terms of the mechanism proposed by *Wilkinson et al.*[35] for the hydroformylation of olefins with $HRhCO(PPh_3)_3$ or $HRh(CO)_2(PPh_3)_2$.



(47) *(48)* *(49)* *(43)* *(46)* *(50)* *(R)-(45)*

PR_3 = *(S)-(44)*

Similarly to an enzyme, the chiral catalyst *(46)* can differentiate between the enantiotopic sides of the prochiral olefin. In the case of *(S)*-(+)-*(44)* as ligand PR_3 of the coordinative unsaturated complex *(46)*, styrene *(43)* preferably adds at the side unshielded by the phenyl group. A Rh-π-complex *(47)* is formed and is rapidly converted into a complex *(48)* containing a Rh-alkyl bond. The absolute configuration of the 2-

phenylpropanal is thus established, since CO is inserted in the *cis* position [*(48)*→*(49)*]. The rate determining step of the reaction is cleavage of the acylrhodium complex *(49)* by hydrogen: *(R)*-(−)-*(45)* and the tetrahedral hydrido complex *(50)* are formed, which after uptake of CO to give the complex *(46)* can further add styrene.

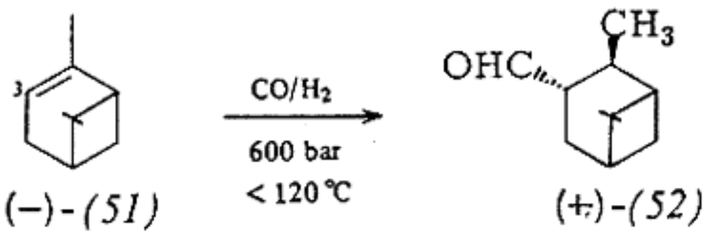
A mechanism involving replacement of one of the two chiral phosphane groups by a carbonyl group in the reaction *(46)*→*(50)* leads to the same result.

With *(S)*-phosphanes, the *(R)*-aldehyde is formed. It is immediately apparent that the arrangement of the groups in the chiral 2-phenylpropanol *(45)* pre-images to a certain extent the groups in the chiral phosphane. With *(S)*-(+)-*(44)* or the corresponding isopropyl compound as complex ligand the enantiomeric purity of the products is *ca.* 20% and 30%, respectively.

The asymmetric hydroformylation of prochiral olefins has so far found no use in industry. One reason for this is the low enantiomeric purity—also observed by other authors[36–39]—of the products obtained from the substrates hitherto examined. Hence, this method is at the moment considered impracticable for the industrial production of optically active intermediates which could be used for optical resolution or asymmetric syntheses.

7. Optically Active Intermediates *via* Hydroformylation of Unsaturated Chiral Natural Products

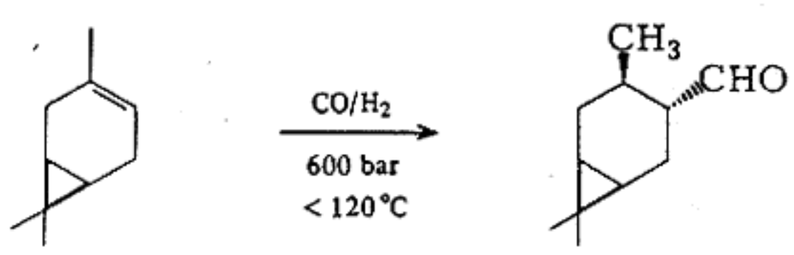
(−)-α-Pinene *(51)*, which is available in large amounts from the cluster pine *(Pinus Pinaster* Sol.), is hydroformylated with rhodium catalysts in a diastereoselective synthesis to (+)-3-pinanecarbaldehyde *(52)*[45]. (+)-α-Pinene from the Aleppo pine (*Pinus Pinaster* Mill.) affords (−)-3-pinanecarbaldehyde[40].



(−)-*(51)* (+)-*(52)*

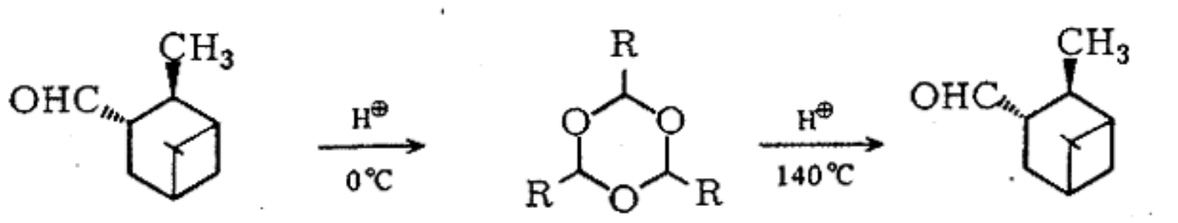
The formation of the reaction products can be explained by the fact that the intermediary alkylrhodium complex evades as far as possible steric hindrance by the isopropylidene bridge and the methyl group. The least hindered position is the equatorial one on the carbon atom 3 of the α-pinene *(51)*. The *cis* addition of CO and H_2 then forces the methyl and formyl group likewise to take up an equatorial position in the 3-pinanecarbaldehyde *(52)*. Depending on the reaction conditions the selectivities are up to 85%. The most important by-products are isomeric aldehydes, which are derived from the β-pinene formed during the reaction by isomerization of the double bond. In the analogous hydroformylation of (+)-3-carene, (+)-*(53)*, the reaction proceeds with a selectivity of only 60–65% to the (+)-2-caranecarbaldehyde (+)-*(54)*[41] owing to comparably little steric hindrance by the isopropylidene bridge.

The enantiomeric purity of the (−)- or (+)-3-pinanecarbaldehyde *(52)* corresponds to that of the α-pinene employed (70–85%). Enantiomerically pure 3-pinanecarbaldehyde is obtained by acid-catalyzed trimerization in the presence of



(+)-*(53)* (+)-*(54)*

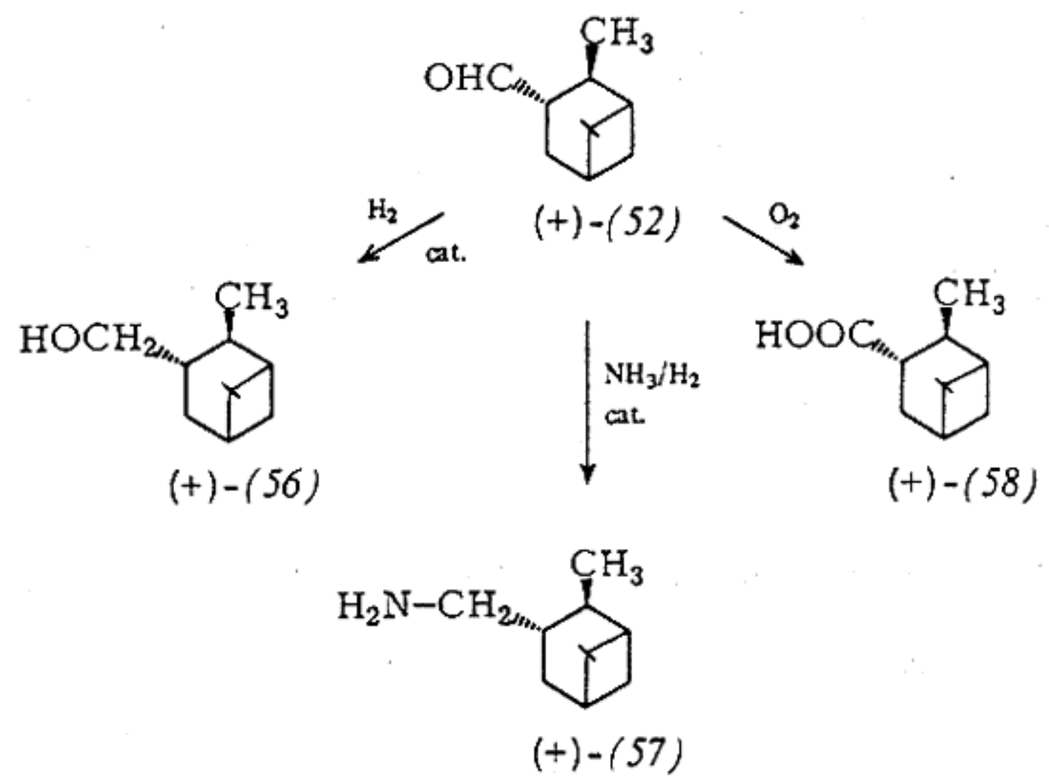
solvents[42]; only one enantiomer is thereby preferentially trimerized to the crystalline compound *(55)*. This is isolated and then cleaved again in the presence of acids to 3-pinanecarbaldehyde.



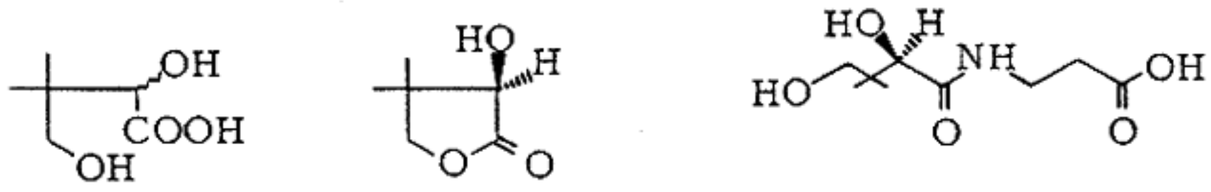
enantiomeric purity 70-85% *(55)* enantiomeric purity ≈100%

R = (+)-3Pinanyl

The optically active pinanecarbaldehydes are very stable against racemization. They can be hydrogenated, aminohydrogenated, or oxidized with retention of configuration by the usual industrial methods.



(+)-3-Pinanylmethanol *(56)*, (+)-3-(pinanylmethyl)amine *(57)*, and (+)-3-pinanecarboxylic acid *(58)* are configurationally stable, optically active intermediates which can be used for enantiomerization and asymmetric syntheses. For example, the amine (+)-*(57)* forms very easily separable diastereomeric salts with DL-pantoic acid *(59)*.



(59) *(60)* *(61)*

Thus, D-(−)-pantolactone *(60)*, a precursos of D-pantothenic acid *(61)*, is obtained in 90% yield and in very high enantiomeric purity[43,44].

8. Outlook

The rhodium-catalyzed hydroformylation of special olefins for the production of aldehydes is a versatile method for unconventional solutions of problematic syntheses in the fine chemicals industry. The possibilities of this method range from simple aliphatic aldehydes to chiral compounds. A dis-

advantage, however, is that not all of the necessary starting olefins are avilable on an industrial scale and that, with higher concentrations of catalyst, the expensive and relatively scarce rhodium must be recycled. However, in spite of these problems still further new syntheses with rhodium-catalyzed hydroformylation intermediates are to be expected in the future.

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